CLINICAL STUDY PROTOCOL

ICTU Adopted

Study Title: A single a**r**m phase IIa study (with combination safety run-in) to assess the safety and efficacy of **A**Z**D**4547 **i**n **c**ombination with either **a**nastrozole or **l**etrozole in ER positive breast cancer patients who have progressed on treatment with anastrozole or letrozole - **RADICAL**

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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or term	Explanation
AE	Adverse event
AI	Aromatase inhibitor
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{(0-t)}$	Area under plasma concentration-time curve from zero to time t
AUC_{ss}	Area under plasma concentration-time curve during any dosing interval at steady state
AZ	AstraZeneca
bd	Bis in Die (twice daily)
C_{max}	Maximum plasma (peak) drug concentration after single dose administration
$C_{ss, max}$	Maximum (peak) steady state drug concentration in plasma during dosing interval
$C_{ss, min}$	Minimum (trough) steady state drug concentration in plasma during dosing interval
CI	Chief Investigator
CR	Complete response (RECIST)
CRF	Case report form
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Averse Events
ctDNA	circulating tumour specific DNA
CV	Coefficient of variation
CYP450	Cytochrome P450
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ECG	Electrocardiogram
ER+	Oestrogen receptor positive
FFPE	Formalin Fixed Paraffin Embedded

FGF	Fibroblast growth factor
FGF23	Fibroblast Growth Factor 23
FGFR	Fibroblast Growth Factor Receptor
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
IC_{50}	Concentration of a drug causing half maximal inhibitory effect
IDMC	Independent Data Monitoring Committee
ICTU	Imperial Clinical Trials Unit
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITTS	Intention to treat analysis set
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
mm	Millimetre
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NCCN	National Comprehensive Cancer Network
NE	Non-evaluable (RECIST)
NSAI	Non-steroidal aromatase inhibitor
NTL	Non-Target Lesion
OCT	Optical Coherence Tomography
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression Free Survival
PI	Principle Investigator
PK	Pharmacokinetic
PD	Pharmacodynamic
PPS	Per protocol analysis set

PR	Partial response
QA	Quality assurance
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RPED	Retinal pigmented epithelium detachment
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease (RECIST)
SOP	Standard Operating Procedure
SRC	Safety Review Committee
SRIS	Safety run-in analysis set
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
t_{max}	Time to reach peak or maximum concentration following drug administration
TMG	Trial Management Group
TSC	Trial Steering Committee
$t_{ss\ max}$	Time of maximum concentration at steady state
TL	Target Lesion
TSA	Tumour size assessment
ULN	Upper Limit of Normal

TRIAL SUMMARY

Title:

A single arm phase IIa study (with combination safety run-in) to assess the safety and efficacy of AZD4547 in combination with either anastrozole or letrozole in ER positive breast cancer patients who have progressed on treatment with anastrozole or letrozole – RADICAL

Primary Objectives:

Safety run-in:

- To assess the safety and tolerability and determine the dose of AZD4547 to be used in combination with a standard dose of anastrozole for the phase IIa part of the study
- To assess the safety and tolerability and determine the dose of AZD4547 to be used in combination with a standard dose of letrozole for the phase IIa part of the study

Phase IIa:

- To assess the efficacy of AZD4547 based on the change in tumour size at 12 weeks (or progression if prior to week 12), when used in combination with either anastrozole or letrozole in ER positive breast cancer patients who have progressed on treatment with either anastrozole or letrozole in any setting.

Secondary Objectives:

Safety run-in

- To assess the pharmacokinetics (PK) of anastrozole or letrozole when given alone compared to in combination with AZD4547
- To describe the PK of AZD4547 when given in combination with anastrozole or letrozole

Phase IIa

- To assess the efficacy of AZD4547 in combination with anastrozole or letrozole as measured by change in tumour size at 6 weeks, 20 weeks, then every 8 weeks, as per study plan.
- To assess the efficacy of AZD4547 in combination with anastrozole or letrozole as measured by tumour response (RECIST criteria) at 6 weeks, 12 weeks, then every 8 weeks, as per study plan.
- To assess the efficacy of the study treatment as measured by the objective response rate (ORR) at 6 weeks, 12 weeks, then every 8 weeks, as per study plan. To assess the efficacy of the study treatment as measured by progression-free survival (PFS)
- To assess the safety and tolerability of AZD4547 in combination with anastrozole or letrozole

Design:

Multi-centre, single arm, open label, phase IIa study (preceded by a safety run-in (Ib) phase)

Study Population:

Safety run-in

Post menopausal women with ER+ breast cancer who are progressing on treatment with either anastrozole or letrozole in the adjuvant or first-

line metastatic setting

Phase IIa
Post menopausal women with ER+ breast cancer who have progressed on treatment with either anastrozole or letrozole in any setting

Sample size:

Safety run-in: 6-24 patients; ***Phase IIa***: 50 patients

Main Eligibility Criteria:

- Written informed consent and ability to comply with study protocol
- Aged ≥ 25 years of age
- Post menopausal women with histological confirmation of breast cancer with documented positive oestrogen receptor status (ER+) of primary or metastatic tumour tissue
- ECOG performance status 0-1 and minimum life expectancy of 12 weeks
- Fulfils criteria for previous treatment of breast cancer:
- **Safety run-in:** Relapse during a single regimen of adjuvant endocrine therapy with either anastrozole or letrozole
  or
- Progression during first line endocrine therapy with anastrozole or letrozole for advanced breast cancer
  Phase IIa: Progressing or progression at some point during breast cancer treatment on endocrine therapy with a non-steroidal AI*
  Co-administration of a targeted agent with the non-steroidal AI is permitted providing all toxicities have recovered to CTCAE Grade 1 or below.
- Prior chemotherapy in the advanced and adjuvant setting is permitted.
- Prior treatment with exemestane with or without everolimus is permitted.
  anastrozole or letrozole does not have to be the most recent therapy
- **Safety run-in:** At least 1 lesion (measurable/non measurable) that can be accurately assessed by CT/MRI/plain x-ray at baseline and follow-up
  Phase IIa: At least 1 measurable lesion ≥ 10mm in longest diameter (or ≥ 15mm in the short axis for nodal disease) at baseline that can be accurately assessed by CT/MRI at baseline and follow up. Patients with bone only metastatic cancer must have a lytic or mixed lytic-blastic lesion that can be accurately assessed by CT or MRI.
- Adequate haematological, hepatic and renal function
- **Phase IIa**: Mandatory provision of tumour biopsy for assessment of oncology biomarkers
- **Safety run-in:** Study entry must be preceded by a minimum of 21 days of anastrozole or letrozole treatment

- **Phase IIa**: No restriction to duration of anastrozole or letrozole treatment prior to study entry.

Treatment:

***Safety run-ins*:** Initially, patients will continue to receive the single agent treatment which they have progressed on: either anastrozole (1mg) or letrozole (2.5mg), orally, once daily for 7 days. N.B. this must be preceded by a minimum of 21 days of anastrozole or letrozole treatment prior to study entry.

Oral AZD4547 will then be added to this ongoing non-steroidal aromatase inhibitor (either anastrozole or letrozole) therapy twice daily but on an intermittent schedule of one week on/one week off.

Phase IIa: Patients will continue or restart the NSAI which they have progressed***** on: either anastrozole (1mg) or letrozole (2.5mg), orally, once daily but together with twice daily AZD4547 (80mg).
AZD4547 will be given on an intermittent schedule of one week on / one week off.

N.B. If 2 or more cases of severe toxicity (leading to permanent discontinuation of study drug) are observed in the first 6 patients, an alternative schedule of 80 mg twice daily, two weeks on / one week off will be considered but in context of emerging data from other AZD4547 studies which may suggest that this is a better tolerated schedule.

*****Prior to study entry, patients must have taken anastrozole or letrozole at some stage in their treatment to date for breast cancer; and shown evidence of resistance to this therapy. The NSAI does not have to be the most recent line of treatment.

Primary Endpoint:

Safety run-in:

- Safety and tolerability as assessed by Dose Limiting Toxicities (DLTs)

Phase IIa:

- Change in tumour size at 12 weeks (or progression if prior to week 12)

Secondary Endpoints:

Safety run-in:

- Pharmacokinetic (PK) parameters of anastrozole or letrozole when given alone and in combination with AZD4547
- PK parameters of AZD4547 when given in combination with anastrozole or letrozole.
- Safety and tolerability as assessed by adverse events (AEs)

Phase IIa:

- Change in tumour size at 6 weeks, 20 weeks, then every 8 weeks, as per study plan
- Tumour response RECIST criteria with 4 categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)
- Objective response rate (ORR) with 2 categories: CR or PR, SD or PD
- Progression-free survival (PFS) is time from study entry to PD (RECIST)

Exploratory Endpoints:

- To collect and store plasma, serum and archival tumour samples or paired tumour biopsies, and analyse surplus blood or tissue, if available, for potential future exploratory research into factors that may influence development of cancer and/or

response to AZD4547 (where response is defined broadly to include efficacy, tolerability or safety)

- To investigate PK/PD relationships including serum FGF23, serum phosphate levels, serum FGF-2 (Safety run-in only)
- To analyse a range of oncology biomarkers, which may correlate with drug response
- To investigate the association between FGFR1 FISH score and the above primary and secondary efficacy endpoints (Safety run-in only)

1. BACKGROUND AND RATIONALE

1.1. Breast Cancer

Breast cancer is the second commonest cancer killer in women accounting for 12,000 deaths per year in the UK. The treatment of breast cancer is determined by the extent of the disease and a variety of other prognostic factors, including hormone receptor status. The most important factor determining response to hormonal manipulation is the presence of the oestrogen receptor (ER) in the target tissue[1]. The choice of treatment sequence is complex and dependent on a number of factors, including prior endocrine treatments received. The National Comprehensive Cancer Network (NCCN) advise that a sequence of up to 3 endocrine therapies may be appropriate before using cytotoxic chemotherapy for advanced disease[2]. The choice of first endocrine therapy is generally an anti-oestrogen such as tamoxifen or a non-steroidal aromatase inhibitor (AI) such as anastrozole or letrozole. Options for subsequent endocrine therapy include a steroidal AI such as exemestane or a selective oestrogen receptor down-regulator such as fulvestrant[3]. Irrespective of the treatment sequence, a number of patients will experience disease progression and therefore there remains a need to identify further treatment options for those patients who progress on endocrine therapy. One approach to this is to elucidate the causes of resistance to endocrine therapy so that agents can be developed which reverse endocrine resistance. Consequently, an improved understanding of the disease biology underlying this resistance is required.

Recent work has suggested that Fibroblast Growth Factor Receptor (FGFR) signalling triggered by fibroblast growth factors (FGFs) such as FGF-2 may be important. Indeed, addition of FGF-2 to breast cancer cell lines in vitro impairs the effects of non-steroidal AIs and tamoxifen whilst downregulation of FGFR1 by siRNAs sensitises breast cancer cells to these agents[4]. Moreover, FGFR1 over-expression in breast cancer is associated with poor prognosis[4]. The effects of FGF-2 in promoting resistance are not confined to anti-oestrogens or to breast cancer; it can also induce resistance to multiple cytotoxic drugs in breast and several other common cancers including lung cancer[5,6]. Our work shows that this growth factor activates MEK/Erk signalling and triggers phosphorylation and inactivation of the pro-apoptotic protein Bad. In addition, FGF-2 also upregulates the translation of several antiapoptotic proteins including Bcl-2, Bcl-XL, XIAP and cIAP1/2, in both cancer and model cell systems[6-8]. These pro-survival effects occur in MCF-7 cells that do not demonstrate FGFR amplification[4,6] (and our unpublished observations). However, about 8-20% of breast cancers display fluorescence in situ hybridisation (FISH) levels equal to 6 for FGFR1 amplification which correlates with early relapse and poor survival particularly in ER positive breast cancer[4]. This suggests that patients with ER positive breast cancer that have FGFR1 amplification might be particularly likely to benefit from FGFR inhibitor based therapies. Nevertheless, the fact that MCF7 cells that lack FGFR amplification are also sensitive to the effects of FGFR downregulation or inhibition[4,6,9] (and our unpublished observations) indicates that patients with less or no FGFR amplification may still benefit from such a therapeutic approach. Moreover, emerging data from other AZD4547 studies in a variety of tumour types have also shown that FISH6 FGFR1 amplification may not be necessary for response. Thus as we begin to study the potential efficacy of FGFR inhibitors in breast cancer, it would be important to determine whether FGFR1 amplification is really necessary as a determinant of disease response in ER positive disease.

1.2. Investigational Agent

AZD4547 is a potent and selective inhibitor of FGFR-1, 2 and 3 receptor tyrosine kinases (enzyme and cellular phosphorylation endpoints), and has a significantly lower potency for inhibition of IGF1R and KDR.

The FGFR family consists of four members each composed of an extracellular ligand binding domain, a trans-membrane domain and an intracellular cytoplasmic protein tyrosine kinase domain. Receptor activation leads to the recruitment and activation of specific downstream signalling partners that participate in the regulation of diverse processes such as cell growth, cell metabolism and cell survival. Dysregulation of the FGFR pathway via genetic modifications of FGFR-1, 2, 3 or 4, including amplification, translocation and mutations have been described in a range of tumour types including breast cancer, gastric cancer and multiple myeloma. Non-clinical data indicate the presence of such modifications confers sensitivity to FGFR inhibitors. Inhibition of FGFR mediated signalling can result in an anti-proliferative and/or pro-apoptotic activity, may have an anti-angiogenic effect, and may play a role in resistance to vascular endothelial growth factor (VEGF) inhibitor therapy. Therefore AZD4547 may have the potential to provide clinical benefit in a variety of advanced solid malignancies which have a FGFR-dependent mechanism.

1.3. Non-clinical Studies

1.3.1. In Vitro Studies

The MDA-MB-134 cell line is FGFR1 amplified (FISH=6) and the SUM52-PE cell-line is FGFR2 amplified (FISH=6) and in both lines this correlates with high expression at the protein level of the relevant FGFR. In both of these FGFR amplified cell-lines AZD4547 is a potent inhibitor of cell growth.

In addition, in low serum conditions, FGF-ligand can stimulate the growth of other breast cancer cell-lines, which do not carry an FGFR gene amplification and hence express significantly lower levels of FGF receptors, examples being MCF7, ZR-75-1 and HCC1187 cells and in these cell-lines AZD4547 inhibits FGF-stimulated proliferation (IC_{50} = 12nM, 36nM and 11 nM for inhibition of FGF-stimulated proliferation in MCF7, ZR-75-1 and HCC1187 respectively) as well as the stimulation of the downstream signalling markers phosho-Erk and phosho-FRS2.
AZD4547 did not produce any measureable in vitro inhibition of P-gp transport and as such would not be expected to cause any drug-drug interaction with substrates of this transporter in patients. (See Investigator Brochure (IB) for further details).

1.3.2. In Vivo Studies

There are no AZD4547 data for *in vivo* activity against breast cancer xenografts/models, but the *in vivo* single agent activity has been validated in several other tumour types.

1.4. Clinical Studies

Recruitment to Study D2610C00001, Study D2610C00002, Study D2610C00003, and Study D2610C00004 is complete.
Study D2610C00001, an open-label, multi-centre, dose escalation Phase I clinical study designed to assess the safety, tolerability, pharmacodynamics, PK and to determine the maximum tolerated dose (MTD) and / or recommended dose of AZD4547 in advanced cancer patients who have progressed following standard therapy or for whom no standard therapy exists, is in the reporting phase.

Study D2610C00003*****, a randomised double-blind Phase IIa study (with combination safety run-in) to assess the safety and efficacy of AZD4547 in combination with exemestane vs. exemestane alone in ER+ breast cancer patients with FGFR1 polysomy or gene amplification who have progressed following treatment with one prior endocrine therapy (adjuvant or first-line metastatic), is also in the reporting phase Enrolment to Part B of this study has also been terminated (27 March 2014) as recruitment was much slower than predicted, leading to concerns about the feasibility of completing enrolment in a realistic timeframe. This, combined with the limited evidence of clinical activity observed with AZD4547 monotherapy in FGFR-amplified gastric cancer and squamous non-

small cell lung cancer (Study D2610C00004 and Study D2610C00001), resulted in a business decision to terminate enrolment to this study.
*****In response to emerging data, study D2610C00003 has since revised study design and switched from exemestane to fulvestrant as the comparator/combination agent.

Study D2610C00002 (same design as D2610C00001 but in Japanese patients) has completed recruitment and a study report is now available.

Study D2610C00004 (a randomised open-label phase IIa study in AZD4547 monotherapy versus paclitaxel in patients with advanced gastric cancer with tumours with FGFR2 polysomy or gene amplification) was terminated in June 2013; based on the results of an interim analysis. It was concluded that the study was unlikely to meet its primary objective of demonstrating superiority of AZD4547 monotherapy over paclitaxel in patients with gastric cancer with tumours that have *FGFR2* amplification (FISH score 6). A study report is now available.

In the AstraZeneca sponsored clinical development programme to date, a total of 208 patients had received at least a single dose of AZD4547 (either suspension formulation or tablet). From the phase I study, a dose of 80mg bd has been established for continuous dosing with AZD4547. All data presented here are preliminary and un-validated.

- 94 patients had received at least a single dose of AZD4547 in part A (dose escalation phase) of Study D2610C00001. 52 of these patients had received AZD4547 at a dose of 80mg .In Part A, 43 patients received a single dose of AZD4547. Cohorts were dosed with the suspension formulation as follows: 20 mg bd (n=3), 40 mg bd (n=5), 80 mg bd (n=6), 150 mg bd (n=7), 200 mg bd (n=6). Cohorts were dosed with the tablet formulation as follows: 200 mg bd (n=4), 160 mg bd (n=6),120 mg bd (n=6).
- Seven dose limiting toxicities (DLTs) have been reported: increased liver transaminases (80 mg bd), mucositis (120 bd mg) stomatitis (150 mg bd),uncontrolled phosphate (160 mg bd), acute renal failure (160 mg bd, 200 mg bd),increased ALT in association with CTCAE Grade 2 increases in phosphate and calcium:phosphate product (200 mg bd).
- The 160 mg bd dose was declared non-tolerated as 2/6 patients experienced DLTs. The Safety Review Committee decided that the 120 mg bd dose was not sufficiently tolerated to support chronic dosing, although it did not achieve the protocol defined definition of a non-tolerated dose. The MTD for AZD4547 has not been formally defined in this study.
- Part B (safety and tolerability expansion phase) of the study has been completed and 6 patients have been dosed at 80 mg bd continuous dose. No patient experienced a DLT in Part B.
- Part C (safety, tolerability and efficacy expansion phase), exploring the safety, tolerability, PK and preliminary anti-tumour activity of AZD4547 in patients with FGFR1 and/or FGFR2 gene amplified tumours, has now completed. There are 3 cohorts for Part C: Cohort 1 – 20 patients with any solid tumour with FGFR1 or FGFR2 amplification (FISH score 6), Cohort 2 – 15 patients with squamous NSCLC that have tumours with FGFR1 amplification (FISH score 6) and Cohort 3 (enrolment terminated)– 10 patients with advanced gastric adenocarcinoma (including adenocarcinoma of the lower third of the oesophagus or the gastro-oesophageal junction) with tumours that have FGFR2 amplification (FISH score 6). A total of 45 patients have been dosed at 80 mg bd (continuous dose). No patient had a DLT in Part C. Enrolment to Cohort 3 in Part C was terminated early due to review of the data from Study D2610C00004.

- 34 out of 40 patients in Part C had discontinued from the study, 22 patients due to disease progression, 8 patients due to an AE, 3 patients due to patient decision, and 1 patient due to "Other" (death).

To date, the majority of adverse events experienced by patients receiving AZD4547 have been CTCAE Grade 1 or 2 in intensity. The most commonly reported AEs (overall; all doses in all parts of the study) were constipation (43 patients); xerostomia (40 patients); stomatitis (39 patients); diarrhoea (33 patients); alopecia (32 patients); vomiting (31 patients) and decreased appetite (31 patients).

- There have been 49 SAEs reported by 25 patients; this includes 1 SAE (respiratory distress) in 1 patient who was ongoing in Part C after the date of database lock for the study. Nineteen SAEs in 12 patients were considered by the reporting investigator to be related to treatment with AZD4547. Asthenia, blood creatinine increased, chorioretinopathy, dehydration, dyspnoea, general physical health deterioration, renal failure, sepsis, and vomiting are SAE terms reported on more than one occasion.
- Four deaths related to an AE had been reported: unknown cause; euthanasia and respiratory distress, none were considered related to AZD4547 and sepsis with respiratory failure' which the reporting investigator considered was related to treatment with AZD4547. The patient had paracentesis for ascites 16 days prior to the events that may have triggered the sepsis with respiratory failure, pericardial effusion and pleural effusion. The patient's underlying metastatic gastric carcinoma with ascites also provides an alternative explanation for the occurrence of the events.

A total of 20 from 82 eligible patients have had a best response of partial response (1 patient) or prolonged stable disease (stable disease ≥7 weeks in Part A and Part B [8 patients] and stable disease ≥6 weeks in Part C [11]; total 19 patients) based on tumour assessment by RECIST 1.1. Note that Part C cluster patients are not included in the efficacy analyses.

At study completion, a total of 34 patients had received at least a single dose of AZD4547 in the Japan dose escalation study (D2610C0002).

- Cohorts were dosed with the tablet formulation as follows: 40 mg bd (n=3), 80 mg bd (n=10), 120 mg bd (n=6) and 160 mg qd (n=15).
- No DLTs have been reported to date, and the MTD has not yet been defined.
- A total of 10 patients received at least a single dose of AZD4547 at 80 mg bd.
- Thirty four patients had discontinued from the study, 19 patients due to disease progression, 9 patients due to AEs and 6 patients due to patient decision.
- All but 1 patient had reported at least one AE at the data cut-off. To date, the majority of AEs experienced by patients receiving AZD4547 have been CTCAE Grade 1 or 2 in intensity.
- The most commonly reported AEs at the AZD4547 80 mg bd dose from Part A and Part B were stomatitis (6 patients), xerostomia (5 patients), dysgeusia (5 patients), nausea (4 patients), decreased appetite (3 patients), diarrhoea (3 patients), epistaxis (3 patients), hyperphosphataemia (3 patients), malaise (3 patients), neutropenia (3 patients), and vomiting (3 patients).
- Four SAEs were reported by 3 patients: stomatitis (1 patient); nausea (1 patient); decreased appetite (2 patients). No deaths due to an AE have been reported during the study treatment.

- The best objective response observed (in the opinion of the investigator) was prolonged stable disease (stable disease≥4weeks), recorded in 22/34 patients.

Study D2610C00003 had 2 parts; a safety run-in (Part A: AZD4547 in combination with exmestane) with 4 cohorts and a randomised Phase IIa study (Part B), using AZD4547 in combination with fulvestrant.

A total of 31 patients with ER+ breast cancer received at least a single dose of AZD4547 in combination with exemestane 25 mg in the safety run-in period. In all cohorts of the safety run-in period patients have received exemestane 25 mg for 7 days prior to co-administration of exemestane 25 mg with AZD4547 bd.

- In the first cohort (AZD4547 80 mg bd continuous), all 5 patients had discontinued from AZD4547. Three due to disease progression and 2 due to an AE (nail discolouration and oedema peripheral in 1 patient; depression and neuralgia in 1 patient). No DLTs had been reported to date.
- Although the 80 mg bd AZD4547 cohort did not fulfil the protocol definition of a non-tolerated dose (2/6 patients experiencing a DLT within the 21-day combination evaluation period), the Safety Review Committee decided that the 80 mg bd dose was not appropriate for chronic dosing in this patient population due to the emerging tolerability profile.
- In the second cohort (AZD4547 40 mg bd continuous) , all 5 patients had discontinued the study (4 patients have discontinued due to disease progression and 1 patient due to an AE (chorioretinopathy)
- Twelve patients had been recruited in cohort 3 (80 mg bd intermittent schedule 1 week on AZD4547 and 1 week off treatment). All patients had discontinued the study; 6 patients due to disease progression, 5 due to AEs (dizziness, renal failure; retinal detachment and detachment of retinal pigment epithelium [2 cases]), and 1 due to patient decision.
- Nine patients had been recruited to Cohort 4 (80 mg bd intermittent schedule 2 weeks on AZD4547 and 1 week off treatment). Seven of the 9 patients have discontinued the study (3 patients due to disease progression and 2 due to AEs [detachment of retinal pigment epithelium and lethargy]) and 2 patients are ongoing.
- Part B, nine patients with ER+ breast cancer have received at least a single dose of AZD4547 (80 mg bd continuous dosing) in combination with fulvestrant 500 mg.
- To date, the majority of AEs had been CTCAE Grade 1 or 2 in intensity.
- In Part A the most commonly reported AEs were alopecia (19 patients), xerostomia (17 patients), dysgeusia (16 patients), constipation (12 patients), diarrhoea (11 patients), dry skin (11 patients) and nausea (11 patients). Data from Part B not available at this time.
- The recommended dose for the Phase IIa Period (AZD4547 80 mg bd 2 weeks on/ 1 week off) was based on an analysis of data from the safety run-in period. The most commonly reported AEs in the 9 patients receiving this treatment dose and schedule have been: dysgeusia (6 patients), alopecia (5 patients), nausea (5 patients), decreased appetite (4 patients), xerostomia (4 patients), and nail disorder (4 patients).
- There had been 20 on treatment SAEs reported from 11 patients. In Part A, these were neutropenic sepsis; anaemia; pleural effusion; device deposit issue; renal failure; asthma; dyspnoea; jugular vein thrombosis; VIIth nerve paralysis; pyelonephritis; dizziness; troponin increased; lower respiratory tract infection;; oesophageal achalasia, stomatitis and diarrhoea. Seven of these SAEs (device deposit issue, diarrhoea, dizziness, oesophageal achalasia, renal failure, stomatitis, troponin increased) were considered by the reporting investigator to be related to treatment with AZD4547).

- In Part B, theses were dizziness, inflammation, psoriatic arthropathy, and gait disturbance. None were considered by the reporting investigator to be related to treatment with AZD4547.
- No deaths due to an AE have been reported during the study treatment.

At the time of study closure, a total of 40 patients with advanced gastric cancer had received study treatment of AZD4547 (80 mg bd 2 weeks on and 1week off schedule) in the D2610C00004 study

- Thirty nine patients had discontinued the study treatment (31 due to disease progression, 3 due to AE, 2 due to patient decision, 2 due to death and 1 due to performance score of 3) and 1 patient was ongoing.
- To date, the majority of AEs experienced by patients receiving AZD4547 have been CTCAE Grade 1 or 2 in intensity. Most commonly reported AEs (of any grade) reported for patients receiving AZD4547 were: decreased appetite (16 patients), asthenia (11 patients), nausea (10 patients), constipation (10 patients), stomatitis (10 patients), abdominal pain (9 patients), abdominal pain upper (9 patients), xerostomia (9 patients), and vomiting (8 patients).
- Twelve on-treatment or post-treatment SAEs had been reported for 8 patients receiving AZD4547. One AZD4547 treatment-related SAE was reported, stomatitis in 1 patient.

Two deaths related to an AE had been reported (intestinal haemorrhage and arterial disorder), neither considered related to AZD4547.The adverse events considered to be associated with the administration of AZD4547 can be found in section 5.4 of the current IB.

1.5. Aromatase Inhibitors

1.5.1. Pharmacokinetic Considerations of the Combination Therapy

The pharmacokinetics and metabolism of letrozole and anastrozole are well understood [10]. A key question for us is whether we anticipate any interactions with AZD4547. Letrozole with continuous oral dosing reaches a steady state at 2-6 weeks. The drug is cleared through hepatic metabolism via CYP3A4 and CYP2A6 and subsequent urine clearance. Anastrozole reaches a steady state after 7 days and is 40% plasma protein bound. It is also metabolised in the liver and cleared via the kidneys. It has no effect on CYP2A6 but can inhibit CYP1A2 and CYP2C8 albeit at higher concentrations (2 logs) than clinically used. AZD4547 binding to human serum albumin and to human α1-acid glycoprotein was 93.2% and 69.6% respectively. One of the principal metabolites formed by human hepatocytes was found in the rat, but other human metabolites were not formed in significant amounts in any non-clinical species. CYP3A4, CYP3A5 and CYP2D6 are likely to be responsible for the metabolism of AZD4547 in vivo, although CYP1A1 turnover may be important in smokers. AZD4547 produced competitive inhibition of CYP3A4/5 using testosterone as the probe substrate, but not with midazolam, and it was also shown to be a time dependent inhibitor of the same isozymes.

From the above, we do not anticipate any problems with the combination of anastrozole and AZD4547. However, there is a small possibility that letrozole and AZD4547 may interact through one of their common metabolising enzymes CYP3A4. Nevertheless, Astrazeneca have in house data showing that other drugs using this pathway are unaffected by AZD4547 suggesting that this issue may not be clinically relevant. On this basis, the safety run-in part of the trial has been designed to start using the pharmacologically active, tolerated, dose defined from the currently running Phase I AZD4547 trial with the usual clinical dosing used for either anastrozole or letrozole.

1.6. Rationale

There is an increasing body of evidence implicating FGFs such as FGF-2 and their receptors in cancer biology, whereby these growth factors /receptors drive cancer cell proliferation, invasion, and

survival as well as facilitating neoangiogenesis. More recently, it has become clear that FGF-2 and its receptors FGFR1 and FGFR2 can also induce resistance to multiple chemotherapeutic agents in several cancer types. Consequently, there has been considerable interest in developing selective FGFR inhibitors. The most widely used FGFR inhibitor in preclinical studies has been PD173074. We have shown this to be selective (like AZD4547) and active in blocking the growth of multiple lung cancer cell lines in vitro as well as able to block SCLC xenograft growth in vivo[11] (and data not shown). Moreover, PD173074 blocks chemoresistance in vitro and enhances the effects of chemotherapy in vivo. There is no reason to believe that AZD4547 would behave differently and our preliminary data confirms this in lung cancer cells.

1.6.1. Rationale for use in Breast Cancer

Ectopic over expression/activation of FGFR1 in mammary cells leads to increased proliferation and invasiveness, reduced survival and cell transformation[12] and expression of an FGFR1 transgene in mice caused mammary alveolar hyperplasia and invasive lesions[13]. In the SUM44, MDA-MB-134 and CAL120 cell-lines FGFR1 gene amplification correlates with high levels of FGFR expression and activation of downstream signaling pathways including pErk and pAkt pathways[4,14]. The MDA-MB-134 cell-line is highly dependent upon FGF-ligand for growth and survival and very sensitive to growth inhibition by AZD4547 (IC50 =15nM). Exposure of SUM44 cells to FGF induces resistance to the growth inhibitory effects of tamoxifen and in both this cell-line and CAL120 down regulation of FGFR1 sensitizes to the growth inhibitory effects of tamoxifen treatment[4]. These data suggest that inhibition of FGFR1 can arrest the growth of mammary cells by both endocrine-dependent and endocrine-independent mechanisms. This together with the data presented previously provides a rationale for why AZD4547 should be tested in combination with AIs such as anastrozole and letrozole to see whether it can reverse resistance to these AIs. In addition, one of the key questions as FGFR inhibitors like AZD4547 are developed, is whether amplification of FGFR1 is really necessary to see benefit from this class of agent. Our pre-clinical data suggests that such amplification may not be necessary and this study will therefore also test this hypothesis.

1.6.2. Rationale for Revised Phase IIa Study Design

When this study was originally conceived, the standard of care for post-menopausal women with ER positive advanced breast cancer included letrozole or anastrozole therapy. Once this therapy failed, many women were then given exemestane alone before progressing to chemotherapy. However, the recent results of the Bolero trial[15] and other studies have changed the landscape and currently, many women are now being offered exemestane together with the rapalogue everolimus. This is clearly efficacious but also considerably more toxic than exemestane alone. Consequently, whether this will remain the next line of therapy following resistance to letrozole and anastrozole is very unclear particularly since a number of other novel agents are being studied in this disease setting. Therefore, in discussion with the UK breast community, the Trial Steering Committee (TSC) and Trial Management Group (TMG) felt that the most appropriate design was a simple non-randomised single arm design in which the central hypotheses of whether AZD4547 can re-establish response to either letrozole or anastrozole will be tested and whether FISH6 FGFR1 amplification is necessary for this benefit; there will also be an ongoing appraisal of safety and tolerabilty.

1.6.3. Rationale for AZD4547 Dose and Schedule (Phase IIa)

On completion of the DLT review period, the Safety Review Committee (SRC) reviewed all available safety data from both cohorts in the safety run-in part of the study and made the recommendation that 80mg bd AZD4547 one week on/one week off + NSAI combination will be carried forward to the Phase IIa part of the study.

1.6.4. Risk – Benefit Assessment

Potential Benefits

Dysregulation of the FGFR pathway is observed in a variety of cancers, due to gene amplification, translocations or mutations. Non-clinical data suggests that inhibition of FGFR mediated signalling can result in an anti-proliferative and/or proapoptotic activity and may also have an anti-angiogenic effect.

Potential Risks and their Management
Ocular Toxicity

In the clinical studies conducted to date the adverse events reported regarding the anterior aspect of the eye (dry eyes, blurred vision, conjunctivitis and keratitis) are consistent with the pathological changes that were seen pre-clinically. It is anticipated that patients will report any visual disturbances or discomfort relating to the eye in advance of any significant pathology such as ulceration occurring. The decision to continue on study treatment if mild corneal changes in the eye examination are observed will be left to the Investigator's discretion, since a patient may indicate a wish to tolerate minor discomfort if there is perceived clinical benefit from the therapy. A patient should be immediately withdrawn from study treatment if corneal ulceration occurs, and appropriate expert ophthalmologic consultation should be initiated.

Retinal pigmented epithelium detachment (RPED) has been identified in clinical studies with AZD4547 (45 occurrences as of 04 June 2014). Patients with conditions pre-disposing to the development or re-occurrence of RPED will be excluded from participation in the study. In order to detect this, patients will have a baseline ophthalmologic examination (including OCT scan) prior to initiation of study treatment and approximately monthly for the first 3 months. Thereafter, patients continuing the study treatment will have a full ophthalmological review every 8 weeks (+/- 1 week) until permanent discontinuation of AZD4547. At any other time, abnormal visual symptoms or signs will trigger a full ophthalmological review.

Mineralisation, Particularly in the Heart

The cardiac mineralisation identified in both non-clinical species is thought to be as a direct consequence of elevated serum phosphate levels. The increase in phosphate levels are thought to be pharmacological as a consequence of inhibition of FGF23 modulated phosphate homeostasis in the kidney. In the dog, the increase in phosphate level occurred prior to mineralisation, and at lower doses where no mineralisation occurred. Mineralisation was of low incidence, and was not present following 4 weeks off dose. The clinical studies to date have confirmed the pre-clinical finding of increases in serum phosphate and following review of the data hyperphosphataemia is considered to be an expected event in patients treated with AZD4547. There have been no reports, and no evidence of any soft tissue, including cardiac, mineralisation clinically. However based upon the presumption that increases in phosphate precede mineralisation, patients will be excluded from the study if they have phosphate or calcium levels above the upper limit of normal prior at time of entry. Serum phosphate and calcium are included in the standard clinical chemistry safety bloods which will be assessed on a regular basis. Any patient who experiences a doubling of phosphate from baseline or a corrected calcium:phosphate product >4.5 mmol/L should have phosphate chelation therapy initiated with a non-calcium containing agent, and weekly clinical chemistry assessments performed until resolution of the parameter to below the intervention limit. Investigators must seek appropriate specialist medical consultation (renal or metabolic) to advise on the prescription and titration of phosphate chelation agents, and to raise the patients' awareness of low phosphate diets.

It is likely that mineralisation occurring within the heart will result in functional changes prior to any gross structural changes being apparent by specific imaging technology. Therefore patients will have regular troponin I or troponin T measurements at the same time as the clinical chemistry safety blood measurements. In addition ECGs and MUGA/echocardiograms will be assessed regularly as detailed in the study plan while the patient is on study treatment in order to identify functional changes. The protocol includes standard exclusion criteria for unstable cardiac conditions and risk factors for QTc prolongation.

Renal Toxicity

In clinical studies of AZD4547 in advanced cancer populations there have been 8 renal SAEs in 7 patients. Each case may have an alternative explanation for the events, such as presence of a renal tumour, adrenal metastases, advanced cancer, and a history of listhesis. Analysis of the laboratory values for serum creatinine showed that 30% of patients have had an abnormal serum creatinine value while taking AZD4547 or during the follow-up period. Of these, 19 patients had an improvement in the serum creatinine level when AZD4547 was stopped either temporarily or permanently.

Although there are multiple alternative explanations for the observed elevated creatinine levels (such as advanced cancer patients with disease progression, nephrotoxic concomitant medications, or a history of renal failure) there appears to be a pattern in many patients where the phosphate rises in tandem with serum creatinine. The magnitude of change is not the same but the general trend upwards or downwards is matched. Intermittent dosing schedules show the effect more clearly, and the pattern can be seen in patients with normal serum creatinine values, as well as those whose creatinine rises above the upper limit of normal.

All patients should be closely monitored for any signs of impaired renal function. Patients should be excluded from the study if they have serum creatinine >1.5 times the upper limit of normal concurrent with creatinine clearance <50 mL/min (measured or estimated by Cockcroft and Gault formula). Serum creatinine and blood urea nitrogen will be included in the standard clinical chemistry safety bloods and will be assessed on a regular basis.

Bone Turnover

Histopathological changes in bone structure have been identified in the rat but not the dog. Similar bone changes have been reported in the literature following administration of another FGFR inhibitor to rats, and have been considered due to a pharmacological effect on growing bones. Patients born with mutations in FGFR genes develop a range of skeletal disorders during childhood such as osteoglyphonic dysplasia, Apert syndrome and hypochondroplastic dwarfism. Only patients over the age of 25 will be permitted to enter the study, in order to exclude individuals who have not completed maturation of their skeleton. Bone adverse events will be reviewed on a case-by-case basis as it is not possible to provide specific stopping criteria given the background of extensive metastatic disease seen with the advanced cancer patient population, which might result itself in pathological fractures and bone pain.

Mouth-related conditions

Events of ageusia, dysguesia, stomatitis/oral mucositis and xerostomia have been reported in the clinical studies to date. In cases of stomatitis particular attention should be given to prophylaxis, maintaining a high standard of oral hygiene with the regular use of antibacterial mouthwashes during the study. Saline nasal sprays may help nasal mucosal dryness and so reduce the incidence of epistaxis.

Dermatological Toxicity

There have been a number of events reported in patients receiving treatment with AZD4547 involving the skin and associated appendages. These include events of dry skin, alopecia, hair changes, trichomegaly and changes to the nails and nail beds.

Diarrhoea

Diarrhoea has been commonly reported in patients receiving AZD4547 across all studies, the majority of which have been non-serious and CTCAE Grade 1. Diarrhoea is therefore considered as an expected event in patients treated with AZD4547. Patients have responded to symptomatic treatment, for example with loperamide.

Neutropenia

Neutropenia and febrile neutropenia are common risk factors for cancer patients receiving chemotherapy treatment. A review of data for patients enrolled in AZD4547 clinical studies has not identified any dose relationship with neutropenia and indicates most events are CTCAE Grade 1 or Grade 2. However, events of CTCAE Grade 4 neutropenia have been reported and were associated with febrile events with the possibility of infection, treatment with antibiotics was given. One patient who died had febrile neutropenia but the investigator considered the patient died as a result of disease progression. Two CTCAE Grade 1 AEs were considered by the investigator to be related to treatment with AZD4547. Two SAEs with element of neutropenia have been reported (1 in Study D2610C00003 and 1 in an Investigator-Sponsored Study); however, these were not considered to be related to AZD4547 treatment.

Any AE of neutropenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTCAE Grade 3 or worse neutropenia occurs. If a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including granulocyte-colony stimulating factor should be given according to local hospital guidelines.

Increases in Transaminases

Increases in transaminases have been reported in the clinical studies to date and following review of the data are considered to be expected events in patients treated with AZD4547 Most of these increases were CTCAE Grade 1 or Grade 2. There was no clear relationship between the dose of AZD4547 and the incidence or severity of the increase in transaminases.

Intermittent dosing schedules have allowed examination of the effect of dechallenge and rechallenge with AZD4547, and while there was some evidence of an effect with AZD4547 in a few patients, overall, there was little difference in the data obtained from dosing with continuous or intermittent schedules. Liver function test abnormalities were most common in patients with liver metastases and in patients with progression of their underlying cancer; multiple concomitant medications in these patients is also a confounding factor.

Studies of AZD4547 include regular measurements of ALT, AST and other hepatic biochemistry parameters. All patients should be closely monitored for any signs of of liver toxicity.

Asthenic Conditions

Literature for multi-targeted kinases suggests there may be an association between asthenic events and the use of FGFR and VEGF inhibitors; however, it is difficult to suggest there is an association directly with FGFR inhibitors.

There is also a suggestion from pre-clinical findings that FGF may modulate some of the metabolic processes such as FGF-19 (ligand for FGFR4) and FGF21 (ligand for FGFR 1, 2, 3, and 4) that can

regulate glucose, lipid, and energy metabolism and cause changes in energy expenditure; this may provide a mechanism for why asthenic events occur with FGFR inhibitors.

Preliminary findings from the data analysed within the AZD4547 clinical studies shows an incidence of asthenic reported terms of approximately 50% within the most frequently prescribed schedule of 80 mg bd continuous cohorts. There is not a dose response for asthenic AEs occurring at higher doses in the continuous schedule. Findings are inconsistent, the proportion of AEs are less severe and frequent in the 120 mg and 200 mg cohorts in comparison with those found in the 20 mg to 160 mg cohorts.

The data for asthenic events for intermittent schedules of 80 mg bd (1 week on/1 week off and 2 weeks on/1 week off) shows an incidence of approximately 45% to 50% and approximately 50% for patients receiving 80 mg continuously. There is also >50% incidence of asthenic conditions reported in the higher dosing cohorts in Study D2610C00001 and D2610C00002.

Across all the studies the time to onset for asthenic conditions overlaps amongst the varying dosing cohorts. This makes it difficult to suggest a causal relationship as the time to onset is not reduced in the higher dosing cohorts and intermittent schedules where patients are off drug for 1 week. Confounding factors such as disease progression, low haemoglobin values, comorbidities such as hypothyroidism, chronic obstructive pulmonary disease, infections and multiple concomitant medications (opiates, antihistamines, anti-hypertensive, anti-nausea) are alternative explanations for asthenic events, but no single factor can explain all cases. Common treatable causes of asthenic conditions (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated in patients with asthenia, fatigue or malaise.

Reproductive Organs

No reproductive toxicology or teratogenic studies have been conducted with AZD4547 to date, and it is unknown whether the drug is excreted in human milk. This study is being conducted in postmenopausal women only and so this is not considered a relevant risk in this study.

Possible Drug Interactions

AZD4547 is a substrate of CYP3A4 and CYP2D6 therefore use of inhibitors/inducers of these isoforms will be excluded from 2 weeks prior to the first dose of AZD4547 and for the duration of study treatment. CYP1A1, an isoform highly inducible by cigarette smoking, is also capable of metabolism of AZD4547 and may lead to lower exposures in smokers, therefore smoking status will be recorded as part of the demographic information for all participating patients. AZD4547 shows weak competitive inhibition of CYP3A4 and is also a time-dependent inhibitor of this isoform. This may lead to reduced metabolism (and increased exposure) of any co-administered drugs that are significantly cleared via this pathway. Concomitant use of medicines significantly metabolised by CYP3A4 will be contraindicated during the course of the study. Use of other agents less significantly metabolised will be permitted with caution if considered clinically indicated for the welfare of the patients, and patients will be closely monitored for possible drug interactions.

Overall Benefit-Risk Assessment

In the advanced cancer setting that has been chosen for this study, prolonged survival rates are very low and there is a large unmet clinical need for novel therapeutic agents.

Although there can be no certainty of clinical benefit to patients, non-clinical data with AZD4547 support the hypothesis that FGFR inhibition may be a valid target for the treatment of tumours driven via this pathway. The non-clinical safety profile has not identified any risks that would preclude

investigation in this setting, and monitoring is in place for those risks deemed to be most likely or serious.

Investigation of AZD4547 in this patient population is justified, based upon the non-clinical safety profile, the limited life expectancy due to malignant disease, and the strength of the scientific hypothesis under evaluation. Thus the benefit/risk assessment for this study supports the oral administration of AZD4547 together with anastrozole or letrozole to patients with advanced cancer, according to the proposed study design.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objectives

Safety run-in

- To assess the safety and tolerability and determine the dose of AZD4547 to be used in combination with a standard dose of anastrozole for the phase IIa part of the study
- To assess the safety and tolerability and determine the dose of AZD4547 to be used in combination with a standard dose of letrozole for the phase IIa part of the study

Phase IIa

- To assess the efficacy of AZD4547, based on the change in tumour size at 12 weeks (or progression if prior to week 12), when used in combination with either anastrozole or letrozole in ER positive breast cancer patients who have progressed on treatment with either anastrozole or letrozole in any setting.

2.2. Secondary Objectives

Safety run-in

- To assess the pharmacokinetics (PK) of anastrozole or letrozole when given alone compared to in combination with AZD4547
- To describe the PK of AZD4547 when given in combination with anastrozole or letrozole

Phase IIa

- To assess the efficacy of AZD4547 in combination with anastrozole or letrozole as measured by change in tumour size at 6 weeks, 20 weeks, then every 8 weeks, as per study plan.
- To assess the efficacy of AZD4547 in combination with anastrozole or letrozole as measured by the tumour response (RECIST criteria) at 6 weeks, 12 weeks, then every 8 weeks, as per study plan.
- To assess the efficacy of the study treatment as measured by the objective response rate (ORR) at 6 weeks, 12 weeks, then every 8 weeks, as per study plan.
- To assess the efficacy of the study treatment as measured by progression-free survival (PFS)
- To assess the safety and tolerability of AZD4547 in combination with anastrozole or letrozole

2.3. Primary Endpoints

Safety run-in

- Safety and tolerability as assessed by DLTs

Phase IIa

- Change in tumour size at 12 weeks (or progression if prior to week 12)

2.4. Secondary Endpoints

Safety run-in

- PK parameters of anastrozole or letrozole when given alone and in combination with AZD4547
- PK parameters of AZD4547 when given in combination with anastrozole or letrozole
- Safety and tolerability as assessed by AE

Phase IIa

- Change in tumour size at 6 weeks, 20 weeks, then every 8 weeks, as per study plan
- Tumour response RECIST criteria with 4 categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)
- Objective response rate (ORR) with 2 categories: CR, PR, SD versus PD.
- Progression-free survival (PFS) is time from study entry to PD (RECIST)

2.5. Exploratory Objectives / Endpoints

- To collect and store plasma, serum and archival tumour samples or paired tumour biopsies and analyse surplus blood or tissue, if available, for potential future exploratory research into factors that may influence development of cancer and/or response to AZD4547 (where response is defined broadly to include efficacy, tolerability or safety)
- To investigate PK/PD relationships including serum FGF23, serum phosphate levels, serum FGF-2 (safety run-in only)
- To analyse a range of oncology biomarkers, which may correlate with drug response
- To investigate the association between FGFR1 FISH score and the above primary and secondary efficacy endpoints (safety run-in only)

3. STUDY DESIGN

This study protocol has undergone peer review as part of the process of endorsement by the Cancer Research UK New Agents Committee

3.1. Overall Study Design

This is a phase IIa (with safety run-in), multi-centre, open label, single arm study of AZD4547 administered orally together with anastrozole or letrozole in ER+ breast cancer patients who have progressed on treatment with anastrozole or letrozole; in adjuvant or first line metastatic (safety run-in only) or any setting (phase IIa only). There are two parts to this study: an initial safety run-in followed by a phase IIa study.

Safety run-in: Two safety run-ins will be conducted to assess the safety and tolerability of AZD4547 in combination with anastrozole and in combination with letrozole. Between 3 and 12 patients will be enrolled into each of the safety run-in parts of the study (i.e. 6 to 24 in total). In both parts, the first cohort will receive 80 mg bd AZD4547. The total number of patients will depend upon the number of cohorts necessary (see Figure 1). A cohort will have a minimum of 3 and maximum of 6 patients (see

Figure 2). The Safety Review Committee (SRC) will determine the dose de-escalation scheme, whether further cohorts are required, and ultimately select the safe and tolerated dose of AZD4547 to be used in the phase IIa study. A different dose level of AZD4547 may be selected for combination with anastrozole than for letrozole.

Phase IIa: 50 patients will be recruited to receive study treatment (see Figure 3).

3.2. Treatment Regimens

Safety run-in:

Initially, patients will continue to receive the single agent treatment which they have progressed on: either anastrozole (1mg) or letrozole (2.5mg), orally, once daily for 7 days. N.B. this must be preceded by a minimum of 21 days of anastrozole or letrozole treatment prior to study entry.

Oral AZD4547 will then be added to this ongoing non-steroidal aromatase inhibitor therapy twice daily but on an intermittent schedule of one week on/one week off.

Phase IIa:

Patients will continue or restart the NSAI which they have progressed***** on: either anastrozole (1mg) or letrozole (2.5mg), orally, once daily but together with twice daily AZD4547 (80mg); the confirmed dose level for AZD4547 determined during the safety run-in part of the study.

*****Prior to study entry, patients must have taken anastrozole or letrozole at some stage in their treatment to date for breast cancer; and shown evidence of resistance to this therapy. The NSAI does not have to be the most recent line of treatment.

AZD4547 will be given on an intermittent schedule of one week on / one week off. This schedule has been well tolerated in the preceding safety run-in part of the study. However, if 2 or more cases of severe toxicity (leading to permanent discontinuation of study drug) are observed in the first 6 patients, the Independent Data Monitoring Committee (IDMC) will consider an alternative schedule of two weeks on / one week off, if emerging data from other AZD4547 studies suggest that this is a better tolerated schedule.

3.3. Study Flow Charts

Figure 1: Study Flow Chart – Safety run-in for both Anastrozole and Letrozole

Cohort 1

7 day NSAI[1] run-in	80mg bd AZD4547 one week on/one week off + NSAI[1] combination

Cohort 2

7 day NSAI[1] run-in	< 80mg bd AZD4547 one week on/one week off + NSAI[1] combination

[1]anastrozole or letrozole

Figure 2: Safety run-in - Dosing Algorithm Within a Cohort

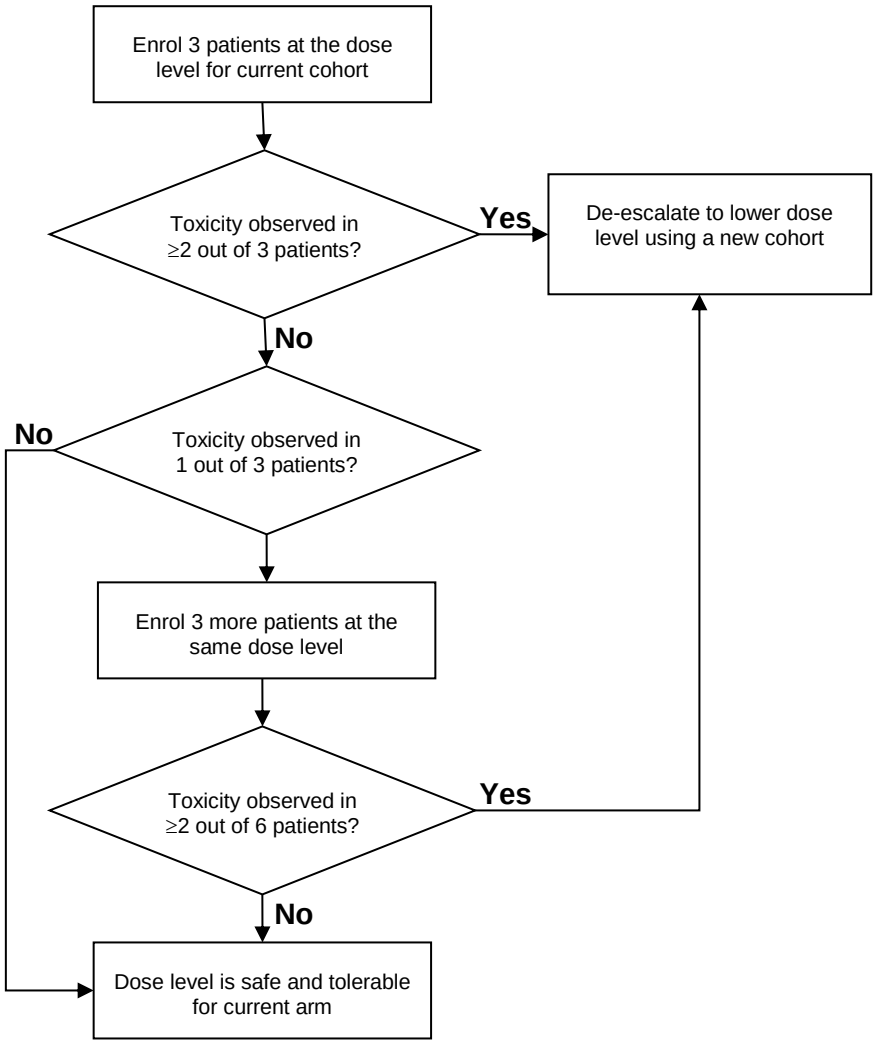
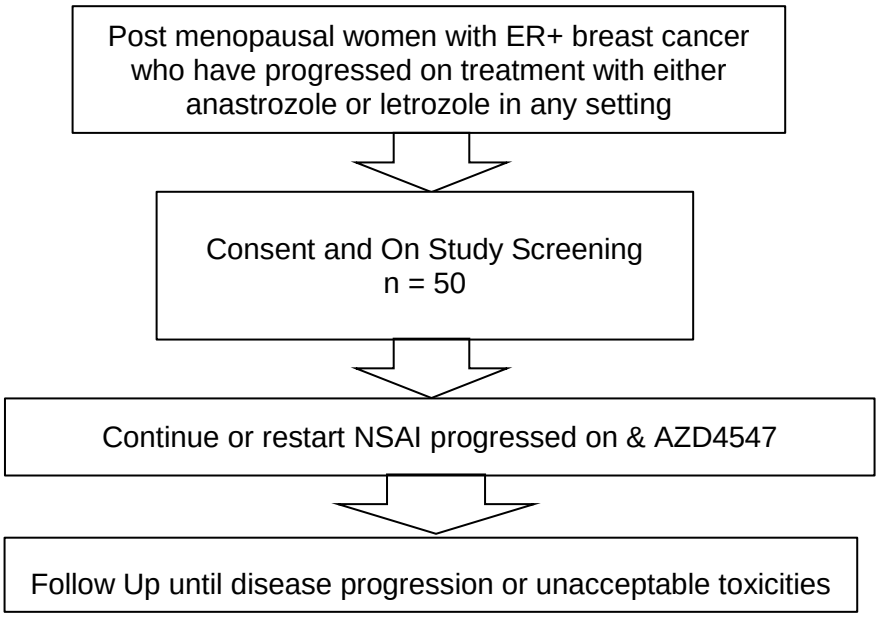


Figure 3: Study flow chart Phase IIa



3.4. Follow-up

All patients on AZD4547 and either anastrozole or letrozole should be followed for 28 days after the last dose of study treatment for complete safety data.

3.5. Study Termination

The study will be terminated when:

- All patients on AZD4547 and either anastrozole or letrozole combination therapy have permanently discontinued study medication due to progression or unacceptable toxicity, and completed 28 days follow-up for collection of safety data

3.5.1. Treatment after Study Termination

Following participation in the study, patient care will be decided by their local doctor according to usual practice.

4. PATIENT SELECTION AND RECRUITMENT

4.1. Screening and Enrolment

Each patient will undergo screening during the 28 days prior to admission to confirm eligibility. Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided they comply with the protocol specified timelines. Written informed consent will be obtained before the subject undergoes any study specific procedures.

Each potential patient will be assigned a unique identifier number for use during the trial. A complete record of all patients who enter screening for the study, and also those who go on to be enrolled, must be maintained at each site. The local investigator is responsible for ensuring that this record includes the allocated trial ID as well as the patient identifiable data including name, hospital number and date of birth.

Eligible patients who take part in the study must meet all of the listed inclusion criteria and none of the exclusion criteria. NB. Some criteria are relevant for the safety run-in or phase IIa parts of the study only; these are marked accordingly.

4.2. Subject Selection

4.2.1. Inclusion Criteria

Patients must fulfil all of the following criteria.

1. Written (signed and dated) informed consent and be capable of co-operating with treatment and follow-up
2. Aged ≥ 25 years of age (N.B. in line with other studies with AZD4574 and due to concerns of possible effects on the immature skeleton)
3. Post menopausal women. Women will be considered postmenopausal if they have had a bilateral oophorectomy or the following specific requirements apply:

   Safety run-in:
   - Women under 50 years old would be considered post-menopausal if they have been amenorrhoeic for 24 months and have follicle-stimulating hormone (FSH) and oestradiol levels in the post-menopausal range. Patients with prior exposure to depot LHRH analogues must be 24 months or more following the last administration
   - Women aged 50 years and older would be considered post-menopausal if they have been amenorrhoeic for 12 months and patients with prior exposure to depot LHRH analogues must be 12 months or more following the last administration
   - Women rendered amenorrhoeic by adjuvant chemotherapy, who were premenopausal or perimenopausal prior to chemotherapy, must have been amenorrhoeic for at least 24 months

   Phase IIa:
   - Women under 50 years old would be considered post-menopausal if they have been amenorrhoeic for 24 months and have follicle-stimulating hormone (FSH) and oestradiol levels in the post-menopausal range.
   - Women aged 50 years and older would be considered post-menopausal if they have been amenorrhoeic for 12 months
   - Women rendered amenorrhoeic by adjuvant chemotherapy, who were premenopausal or perimenopausal prior to chemotherapy, must have been amenorrhoeic for at least 24 months
   - Perimenopausal women rendered amenorrhoeic from exposure to depot LHRH analogues*

   *Patients must have taken LHRH analogues for at least 6 months

4. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 with no deterioration over the previous 2 weeks and minimum life expectancy of 12 weeks
5. Histological confirmation of breast cancer with documented positive oestrogen receptor status (ER+) of primary or metastatic tumour tissue according to local laboratory parameters
6. **Phase IIa**: Mandatory provision of tumour biopsy for assessment of oncology biomarkers
7. Fulfils criteria for previous treatment of breast cancer*:

   Safety run-in:
   - Relapse during a single regimen of adjuvant endocrine therapy with either anastrozole or letrozole
     or
   - Progression during first line endocrine therapy with a non-steroidal AI for advanced breast cancer**. Co-administration of a targeted agent with the non-steroidal AI is permitted providing all toxicities have recovered to CTCAE Grade 1 or below

     1 prior regimen of chemotherapy in the advanced setting is permitted. Chemotherapy administered in the adjuvant setting is permitted

   Phase IIa:
   - Progressing or progression at some point during breast cancer treatment on endocrine therapy with a non-steroidal AI.*** Co-administration of a targeted agent with the non-steroidal AI is permitted providing all toxicities have recovered to CTCAE Grade 1 or below.
   - Prior chemotherapy in the advanced and adjuvant setting is permitted.
   - Prior treatment with exemestane with or without everolimus is permitted.

   *HER2-positive breast cancer patients should have been offered at least one prior line of HER2 directed therapy
   **Advanced breast cancer: metastatic disease or locally advanced disease which is not amenable to treatment with curative intent
   ***anastrozole or letrozole does not have to be the most recent therapy

8. **Safety run-in:** At least one lesion (measurable and/or non-measurable) that can be accurately assessed by CT/MRI/plain x-ray at baseline and follow up visits

   Phase IIa: At least one lesion ≥ 10mm in the longest diameter at baseline (or ≥ 15mm in the short axis for nodal disease) that can be accurately measured with CT/MRI at baseline and is suitable for accurate repeated measurements. Patients with bone only metastatic cancer must have a lytic or mixed lytic-blastic lesion that can be accurately assessed by CT or MRI.
9. **Safety run-in:** Study entry must be preceded by a minimum of 21 days of anastrozole or letrozole treatment

   Phase IIa: No set duration of anastrozole or letrozole treatment prior to study entry.

4.2.2. Exclusion Criteria

1. Treatment with any of the following:
    a. **Safety run-in:** more than 1 regimen of endocrine therapy for advanced breast cancer
    b. previous exposure to any FGFR inhibitor
    c. **Safety run in**: more than 1 prior regimen of chemotherapy for advanced breast cancer.
    d. potent inhibitors or inducers of CYP3A4 or CYP2D6, or substrates of CYP3A4 within 2 weeks prior to first dose of study treatment (3 weeks for St John's Wort)
    e. major surgery within 4 weeks prior to first dose of study treatment
    f. radiotherapy with a wide field of radiation within 4 weeks prior to first dose of study treatment; or radiotherapy with a limited field of radiation for palliation within 2 weeks before the first dose of study treatment
2. With the exception of alopecia, any unresolved toxicities from prior therapy greater than CTCAE grade 1 at time of starting study
3. Spinal cord compression or brain metastases unless asymptomatic, treated and stable and not requiring steroids for at least 4 weeks prior to start of study treatment
4. Any evidence of severe or uncontrolled systemic diseases or active infection
5. Any of the following cardiac criteria:
    a. Resting corrected QT interval (QTc) >470 ms
    b. Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG e.g. complete left bundle branch block, third degree heart block
    c. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval
6. Inadequate bone marrow reserve or organ function as defined by any one of the following parameters:

    Haemoglobin < 9.0 g/dL (<90.0 g/L)
    Absolute neutrophil count (ANC) < 1.5 x 10^9 /L
    Platelet count < 100 x 10^9 /L
    Alanine aminotransferase > 2.5 x ULN if no demonstrable liver metastases or > 5 x ULN in the presence of liver metastases
    Aspartate aminotransferase > 2.5 x ULN if no demonstrable liver metastases or > 5 x ULN in the presence of liver metastases
    Total bilirubin > 1.5 x ULN if no demonstrable liver metastases or > 3 x ULN in the presence of liver metastases
    Creatinine > 1.5 times ULN or creatinine clearance <50ml/min
    Corrected calcium > ULN
    Phosphate > ULN

7. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated IMP or previous significant bowel resection that would preclude absorption of AZD4547 or anastrozole or letrozole
8. History of hypersensitivity to anastrozole or letrozole
9. History of another malignancy within 5 yrs prior to starting study treatment, except adequately treated basal or squamous cell carcinoma of the skin, carcinoma of the cervix and the disease under study

10. Any of the following ophthalmological criteria:*
    - Current evidence or previous history of retinal pigmented epithelium detachment (RPED)
    - Previous laser treatment or intra-ocular injection for treatment of macular degeneration
    - Current evidence or previous history of soft drusen, drusenoid RPE detachment and wet macular degeneration.
    - Current evidence or previous history of retinal vein occlusion (RVO)
    - Current evidence or previous history of retinal degenerative diseases (e.g. hereditary)

    *Patients with uncontrolled glaucoma or intra-ocular pressure >21 mmHg at screening should be referred for ophthalmological management and the condition controlled prior to first dose of study treatment.

11. Concurrent treatment with another investigational agent or use of another investigational agent within 30 days or 5 half lives, whichever is longer, preceding the first dose of study treatment
12. Concurrent treatment with prohibited medications and wash out period for that drug will not have been completed before starting study medication (see Appendix B)

5. STUDY PLAN AND PROCEDURES

5.1. Study Schedules

Scheduled visits are uniquely identified by study period, and day within the period. The combination treatment period of the safety run-in study and the phase IIa study are further partitioned into consecutively numbered treatment cycles of 28 days duration. The period and day when scheduled visits occur, as well as, observations and assessments required during the study are summarised in Table 1 for the safety run-in and Table 2 for phase IIa.

In the phase IIa study, unless indicated otherwise, scheduled assessments may take place within ±1 day of the scheduled day, e.g, laboratory evaluations scheduled for cycle 1 day 7 may take place on cycle 1 day 6 or day 8. Assessment days will all be relative to the start of study treatment, i.e.Cycle 1 Day 1.

If a patient has AZD4547 treatment breaks, please contact the Study Team for advice regarding appropriate timing of PD biomarker assessments. All other assessments, including laboratory safety assessments, vital signs and RECIST should continue to be performed as described in the appropriate sections of the protocol, relative to the baseline assessments

Table 1: Study Plan (Safety run-in)

Study Period	Screening	NSAI[1] monotherapy		AZD4547 + NSAI[1] combination								AZD4547 / NSAI[1] Discont.	28-day follow-up
Cycle	n/a	n/a		Cycle 1				Cycle 2		Cycle 3	Cycle 4 (onwards)		
Activity / Day	-28 to -1	1	7	1	7	15	21	1	15	1	1		
Inclusion/exclusion criteria & informed consent	X												
Demographics	X												
Medical history / Concomitant medical conditions	X	X	X	X	X	X	X	X		X	X	X	
Radiotherapy (previous/current) [2]	X	X	X	X	X	X	X	X		X	X	X	X
Chemotherapy (previous/current)	X												X
Surgical History	X												
Disease Extent/Tumour Characteristics	X												
Concomitant medication	X	X	X	X	X	X	X	X		X	X	X	X
Prohibited medication	X												
Physical examination	X	X	X					X		X	X	X	
ECOG performance status	X	X	X		X	X	X	X		X	X	X	X
Vital signs	X		X					X		X	X	X	X
ECG	X				X			X		X	X	X	
Echo / MUGA scan	X							X[3]				X	
Laboratory evaluations (blood/urine)	X		X		X	X	X	X		X	X	X	X

Study Period	Screening	NSAI[1] monotherapy		AZD4547 + NSAI[1] combination								AZD4547 / NSAI[1] Discont.	28-day follow-up
Cycle	n/a	n/a		Cycle 1				Cycle 2		Cycle 3	Cycle 4 (onwards)		
Activity / Day	-28 to -1	1	7	1	7	15	21	1	15	1	1		
Ophthalmic assessment	X							X		X	X[4]	X	
Treatment compliance			X	X	X	X	X	X		X	X	X	
PI disease status assessments	X								X		X		
Pharmacokinetic sampling			X		X								
Blood sample PD biomarkers	X		X		X	X	X					X	
Treatment dosing		Treatment will be administered according to details in Section 6.2.3.											
DLT assessment				X	X	X	X	X					
Adverse events		X	X	X	X	X	X	X		X	X	X	X
Archival tumour (optional)	X												
Paired tumour biopsy (optional)	X							X[5]					
Pharmacogenetic sample (optional)		X											

[1] Either anastrozole or letrozole

[2] **ONLY** radiation for palliation at focal sites is permitted whilst the patient is on study medication

[3] After the cycle 2, day 1 assessment, MUGA/ECHO should be performed every three months i.e. at the end of cycles 4, 7 etc. and at discontinuation of AZD4547.

[4] After first 3 months of AZD4547, ophthalmological review should be every 8 weeks (+/- 1 week) until permanent discontinuation of AZD4547

[5] The second biopsy should be collected during cycle 2, but as close to completion of 1st cycle of study treatment as possible

Notes: Activities in italic are unique to Safety run-in study.

Table 2: Study Plan (Phase IIa)

Study period	Screening	AZD4547 + NSAI[1] combination									AZD4547 / NSAI[1] Discont.	28-day follow-up
Cycle	n/a	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5 (onwards)		
Activity / Day	-28 to -1	1	8	15	22	1	15	1	1	1		
Inclusion/exclusion criteria & informed consent	X											
Archival tumour[2] sample (mandatory) / exploratory (optional)	X											
Demographics	X											
Medical history / Concomitant medical conditions	X	X	X	X	X	X	X	X	X	X	X	
Radiotherapy (previous/current) [3]	X	X	X	X	X	X	X	X	X	X	X	X
Chemotherapy (previous/current)	X											X
Endocrine Therapy (previous)	X											
Targeted Therapy (previous)	X											
Surgical History	X											
Disease Extent/Tumour Characteristics	X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Prohibited medication	X											
Physical examination	X	X		X		X		X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X		X		X		X	X	X	X	X
ECG	X		X			X		X	X	X	X	
Echo / MUGA scan	X							X[4]			X	

Study period	Screening	AZD4547 + NSAI[1] combination									AZD4547 / NSAI[1] Discont.	28-day follow-up
Cycle	n/a	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5 (onwards)		
Activity / Day	-28 to -1	1	8	15	22	1	15	1	1	1		
Laboratory evaluations (blood/urine)	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic assessment	X					X		X	X[5]		X	
Treatment compliance			X	X	X	X		X	X	X	X	
Tumour assessments as per RECIST 1.1	X						X		X[6]		X	
Blood sample PD biomarkers[7]	X		X	X	X	X		X	X	X	X	
Treatment dosing		Treatment will be administered according to details in Section 6.2.3.										
Adverse events	X[8]	X	X	X	X	X	X	X	X	X	X	X
Paired tumour biopsy (optional)	X[9]				X[10]							
Pharmacogenetics sample (optional)		X										
Circulating tumour specific DNA (ctDNA) (optional)	X[11]	X	X	X	X	X	X	X	X	X	X	X

[1] Either anastrozole or letrozole

[2] If an archival sample is not available, a fresh tumour biopsy sample must be taken.

[3] **ONLY** radiation for palliation at focal sites is permitted whilst the patient is on study medication

[4] After the cycle 3, day 1 assessment, MUGA/ECHO should be performed every three months i.e. at the end of cycles 5, 8 etc. and at discontinuation of AZD4547.

[5] After first 3 months of AZD4547, ophthalmological review should be every 8 weeks (+/- 1 week) i.e. at the end of cycles 5, 7 etc. and at discontinuation of AZD4547

[6] Tumour assessments to be carried out at baseline, week 6, week 12, then every 8 weeks until disease progression or permanent discontinuation of study treatment and finally at AZD4547 discontinuation visit.

[7] If a patient has AZD4547 treatment delays, please contact the Study Team for advice regarding appropriate timing of PD biomarker assessments

[8] AEs collected from the point the patient has been confirmed to be eligible by the RADICAL study team

[9] The first biopsy must only be taken once the patient has been confirmed to be eligible by the RADICAL study team.

[10] The second biopsy **must be taken within 18 hours** of administration of previous AZD4547 dose

[11] Sample to be taken within 1 week of Cycle 1 day 1

5.2. Procedures and Measurements

5.2.1. Demographic Data

Subject date of birth, race / ethnicity and smoking status (smokes or not / habitual or occasional) will be collected at screening.

5.2.2. Medical History / Concomitant Medical Conditions

Both past medical history and concomitant medical conditions will be collected. However, information on radiotherapy, chemotherapy, endocrine therapy, targeted therapy, surgery and medical history of breast cancer including characteristics of the primary and / or metastatic tumour(s), will be documented separately (see below). Concurrent diseases i.e. other medical conditions that are ongoing from the start of the study will be documented in Adverse Events if they worsen.

5.2.3. Previous and Current Radiotherapy

Radiotherapy includes all treatments prior to study entry, whilst on the study, or post permanent discontinuation of study treatment. The following will be collected: site or region (breast, local lymph nodes, distant lymph nodes, bone, brain, or other), setting (neoadjuvant; adjuvant; metastatic), range of field given (wide or limited) and start and end dates of treatment.

5.2.4. Previous and Current Chemotherapy

Chemotherapy includes all treatments prior to study entry or post permanent discontinuation of study treatment. The following will be collected: agent / regimen, site (breast, lung, liver, bone, brain, other) route of administration (IV or tablet), setting (neoadjuvant; adjuvant; metastatic) and start and end dates of treatment.

5.2.5. Endocrine Therapy

Endocrine therapy includes all treatments prior to study entry. The following will be collected: setting (neoadjuvant; adjuvant; metastatic), treatment name (tamoxifen; anastrozole; letrozole; exemestane; other) and start and end dates of treatment.

5.2.6. Targeted Therapy

Targeted therapy includes all treatments prior to study entry. The following will be collected: setting (neoadjuvant; adjuvant; metastatic), treatment name and start and end dates of treatment.

5.2.7. Surgical History

Details of any past surgery that the patient has undergone as part of their treatment of cancer will be collected, i.e. surgical event, reason for surgery and date of surgery.

5.2.8. Medical History of Breast Cancer

Details will be collected on the extent of the patient's disease. The following details will be collected: date of original breast cancer diagnosis, indication of all known sites of locally advanced and metastatic disease, date of most recent progression / recurrence.

5.2.9. Characteristics of the Primary or Metastatic Breast Tumour

The following details will be collected on the characteristics of the tumour: whether tumour was primary or metastatic, location of tumour (if metastatic), histological confirmation of breast cancer tumour (if metastatic), histology of tumour grade, TNM classification of tumour, cancer stage of tumour and receptor status of tumour.

5.2.10. Concomitant Medications

All medications, with the exception of prohibited medications, that are being taken in the 4 weeks prior to starting study treatment (including those during screening) and those taken whilst on study will be documented as a concomitant medication;. The following details will be collected: drug name, reason for therapy, therapy dosage / units, frequency of therapy, route of administration, start and end date of therapy

5.2.11. Prohibited Study Medication

Medications defined as prohibited for use during the study according to Appendix B, “Guidance on Potential Interactions with Concomitant Medications” will be documented during screening. Patients must stop taking any prohibited medications and have completed the required “washout” period prior to starting AZD4547, as per exclusion criterion 12.

5.2.12. Physical Examination

A complete physical examination will be performed, as per local practice at the scheduled visits indicated in the Study Plan. The following examinations should be undertaken: general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, respiratory, abdomen and neurological. The outcome of the examinations will be assessed as normal or abnormal, and whether clinically significant.

5.2.13. ECOG Performance Status

Performance status will be assessed at the scheduled visits indicated in the Study Plan according to ECOG criteria as follows:

0 = Fully active, able to carry on all predisease activities without restriction

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work

2 = Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair 50% or more of waking hours

4 = Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

5 = Death

5.2.14. Vital Signs

Vital signs including weight, pulse and blood pressure will be measured at the scheduled visits indicated in the Study Plan. Vital signs may be assessed at any time during the visit; however, supine blood pressure and pulse should be measured after 10 minutes rest. Height will be measured at initial screening visit only.

5.2.15. ECG

A standard 12-lead ECG will be performed as indicated in the Study Plan. The patient should be examined with the same machine throughout the study.

ECGs will be recorded at the following time points:

- Screening
- Cycle 1 day 8: 2 hours post morning dose of study medication (AZD4547 + either anastrozole or letrozole)
- Cycle 2 day 1 (and each subsequent cycle): any time on the day of assessment

- At discontinuation of AZD4547 + either anastrozole or letrozole therapy

Details of rhythm, ECG intervals and an overall evaluation will be collected.

5.2.16. Echocardiogram and/or MUGA Scan

An echocardiogram and / or MUGA scan to assess left ventricular ejection fraction (LVEF) will be performed at screening, Cycle 3 day 1 (± 1 week), then every 3 months (± 1 week) and finally at AZD4547 discontinuation visit.

5.2.17. Laboratory Evaluations

Blood and urine samples for haematology, clinical chemistry and urinalysis will be taken at scheduled visits and analysed at the local laboratory using standard methods for routine tests. NB. ***On dosing days for all cycles, samples must be taken pre-dose***; as on these visit days, samples must be processed, and results available, prior to administration of the first daily dose of AZD4547 to ensure an assessment of patient suitability to resume dosing is undertaken.

The following variables will be measured:

Clinical Chemistry: ALT, AST, Alkaline phosphatase, Bilirubin (total), Corrected Calcium (total), Creatinine (total), Random glucose, Magnesium, Phosphate, Potassium, Sodium, Troponin I or Troponin T, Urea nitrogen, Albumin

Haematology: Haemoglobin, Leukocyte, Neutrophils, Lymphocytes, Platelets

Urinalysis: Glucose, Protein, Blood

Urinalysis parameters will be measured using a dipstick test. If there are any abnormalities found the urine sample will be sent for Micro Culture Sensitivity Testing

N.B. Management of patients will be according to the corrected calcium result and corrected calcium:phosphate product. Where corrected calcium is not provided by the site laboratory the following formula should be used:
Corrected Calcium = Total Calcium (mmol/L) + ([40 – Albumin (G/L)] x 0.02)

The corrected calcium phosphate product ($Ca:PO_4$) is calculated by multiplying the corrected calcium result by phosphate result:
$Ca:PO_4$ = Phosphate (mmol/L) x ((Total Calcium (mmol/L) + ([40 – Albumin (G/L)] x 0.02))

Laboratory values that have changed significantly from baseline and are considered to be of clinical concern must be recorded as an adverse event and followed up as appropriate.

5.2.18. Ophthalmic Assessment

An ophthalmic assessment will be performed by an ophthalmic expert at screening, Cycle 2 day 1, Cycle 3 day 1 and Cycle 4 day 1 (+/- 3 days), as shown in the study plan (Table 1 and Table 2). Thereafter, patients continuing the study treatment should have a full ophthalmological review every 8 weeks (+/- 1 week) and finally at AZD4547 discontinuation visit. At any other time, abnormal visual symptoms or signs will trigger a full ophthalmological review. Algorithms for further management are provided in Figure 5 and Figure 6 in Section 6.2.8 “Dose Modifications for AZD4547”.

The ophthalmic assessment should be performed on each occasion by the same ophthalmic expert where possible.

The following assessments will be performed in the order stated:

(i) Visual acuity (best corrected) including near and distance vision for each eye separately

(ii) Amsler grid

(iii) Schirmer's test without anaesthesia – read after 5 minutes (this test should be done before instillation of stains or dilatory agents)

(iv) Slit lamp examination:

- Apply 1 drop of 2% fluorescein followed by 1 drop of normal saline
- Measure intra-ocular pressure
- Photograph any abnormalities

(v) Fundoscopy and lens examination following pupil dilatation should be performed using binocular equipment and a 78 dioptre lens (or nearest available equivalent lens)

(vi) OCT scans of the macula area of both eyes should be performed at screening and monthly for the first 3 months on study treatment. After this time, an OCT scan should be performed on the occurrence of clinical symptoms or signs suggestive of RPED. OCT is the preferred methodology for diagnosis of RPED. If OCT is not available as part of local clinical practice, an equivalent alternative diagnostic methodology to screen for RPED should be used.

Clinically significant abnormalities detected during ophthalmic assessments should be reported as AEs. The patient should be managed under the care of a competent ophthalmologist with appropriate medication and followed up until the condition has resolved.

A central review of ophthalmology reports may be undertaken throughout the study.

5.2.19. Treatment Compliance (Patient Diary)

Patients will keep a detailed record of all study medication that they take in their patient diaries. Date and time of administration, drug name and drug dose will be collected.

5.2.20. Principle Investigator Disease Status Assessments (Safety Run-In only)

Principle Investigator (PI) disease status assessments will be performed using CT, MRI or plain x-ray to assess any progression of the patient's disease. The clinician must document: date of assessment, imaging method used (X-ray, CT or MRI), site (breast, lung, liver, pleural effusion, local lymph nodes, distant lymph nodes, bone, brain or other) and outcome of assessment. Disease status assessments will be performed at screening, Cycle 2 day 15 and Cycle 4 day 1.

5.2.21. Tumour Assessments (Phase IIa only)

Tumour assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis. The same method used for assessment at baseline must be used at all subsequent time points.

Tumour assessment will include: if disease is measurable or non-measurable (at least one lesion must be measurable), date of assessment, imaging method used, site (breast, lung, liver, pleural effusion, local lymph nodes, distant lymph nodes, bone, brain or other site), longest diameter of each target lesion and sum of longest diameters for all target lesions.

Patient response to treatment will be assessed using RECIST v1.1 criteria. Tumour size, Progression Free Survival and Objective Response Rate will all be determined.

Tumour Size, will be assessed at baseline and on scans at subsequent time points and recorded as the sum of the longest diameters of the target lesions.

Progression Free Survival (PFS) is defined by the progression criteria of RECIST.

Objective Response Rate (ORR) is defined as the percentage of patients who have at least one visit response of CR or PR prior to any evidence of progression (as defined by RECIST v1.1)

The RECIST v1.1 (January 2009) guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are detailed in Appendix A

Baseline assessment should be performed no more than 28 days before the start of study treatment and ideally as close as possible to the start of study treatment; it should include all areas known for possible breast cancer metastases.

Subsequent tumour assessments will be conducted at week 6, week 12 (primary endpoint) and then every 8 weeks until objective disease progression or cessation of study treatment and finally at AZD4547 discontinuation visit. The window for each assessment is ± 1 week.

Duplicates will be made of all CT/MRI scans. These duplicate scans will be collected to enable an independent review of progression.

5.2.22. Assessment of Archival Tissue Oncology Biomarkers (Phase IIa only)

An archival tissue sample (either from the diagnostic tumour or a metastatic site) in the form of formalin fixed paraffin embedded (FFPE) tumour block will be collected from each patient. If it is not possible to obtain the entire tumour block, 10-20 slides of unstained 5 micron sections may be provided instead.

Provision of a tumour sample is mandatory. If an archival sample is not available, a fresh tumour biopsy sample must be taken. Tumour samples will be tested for oncology biomarkers.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

The following details will be collected: whether archival or fresh tumour, sample tissue type (primary or metastatic), whether representative tumour tissue is present, biopsy site, biopsy type, and histology sample ID.

Archival tumour blocks will be returned to source at the end of the study or earlier, upon request, if required.

5.3. Pharmacokinetics (Safety run-in only)

5.3.1. Collection of Pharmacokinetic Samples

Venous blood samples (2 x 2.7 mL) for determination of concentrations of AZD4547, anastrozole and letrozole in plasma will be taken at the times presented in Table 3 on both day 7 of the NSAI monotherapy and day 7 of cycle 1 of the AZD4547 + anastrozole or letrozole combination therapy. These plasma samples will also be analysed for phosphate and the data used with the AZD4547 PK data to investigate any PK / PD relationship. The date and time of collection of each sample will be recorded.

Table 3: Pharmacokinetic Sampling Schedule for Safety run-in

NSAI[1] monotherapy day 7 and cycle 1 day 7 (AZD4547 + NSAI[1])	
Time relative to dose (hours)	**Time window**
Pre-dose	N/a
0.5	±10min
1	±10min
2	±15min
3	±15min
4	±15min
5	±15min
6	±30min
8	±30min

[1] Either anastrozole or letrozole

The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles. The total number of samples and the total volume of blood taken from each patient will not exceed that presented in Table 4. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.3.2. Determination of drug concentration in PK samples

Samples for determination of AZD4547 concentrations in plasma will be analysed at PRA International, The Netherlands. Samples for determination of anastrozole and letrozole concentrations in plasma will be analysed at Covance, UK, using appropriate bioanalytical methods.

5.3.3. PK Parameter Derivation

The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where possible the following PK parameters will be reported:

Anastrozole

Last day of NSAI monotherapy: $C_{ss,max}$, $t_{max,ss}$, $C_{ss,min}$, $AUC_{(0-8),}$ $AUC_{(0-t)}$, t, AUC_{ss}, CL_{ss}/F, V_{ss}/F, metabolite:parent ratio

Cycle 1 Day 7: $C_{ss,max}$, $t_{max,ss}$, $C_{ss,min}$, $AUC_{(0-8),}$ $AUC_{(0-t)}$, t, AUC_{ss}, CL_{ss}/F, V_{ss}/F, metabolite:parent ratio, ratio of C_{max} Cycle 1 Day 7 / C_{max} last day of NSAI monotherapy, ratio of AUC_{ss} Cycle 1 Day 15 / AUC_{ss} Last day of NSAI monotherapy

Letrozole

Last day of NSAI monotherapy: $C_{ss,max}$, $t_{max,ss}$, $C_{ss,min}$, $AUC_{(0-8),}$ $AUC_{(0-t)}$, t, AUC_{ss}, CL_{ss}/F, V_{ss}/F, metabolite:parent ratio

Cycle 1 Day 7: $C_{ss,max}$, $t_{max,ss}$, $C_{ss,min}$, $AUC_{(0-8),}$ $AUC_{(0-t)}$, t, AUC_{ss}, CL_{ss}/F, V_{ss}/F, metabolite:parent ratio, ratio of C_{max} Cycle 1 Day 15 / C_{max} Last day of NSAI monotherapy, ratio of AUC_{ss} Cycle 1 Day 15 / AUC_{ss} Last day of NSAI monotherapy

AZD4547

Cycle 1 Day 7: $C_{ss,max}$, $t_{max,ss}$, $C_{ss,min}$, $AUC_{(0-8),}$ $AUC_{(0-12)}$, $AUC_{(0-t)}$, t, AUC_{ss}, CL_{ss}/F, V_{ss}/F

5.4. Pharmacodynamics

5.4.1. Saftey Run-In

Blood samples (3 x 5ml) will be collected to provide two samples of plasma and one sample of serum per time point, as indicated in Table 1. These will be analysed for a range of oncology biomarkers including FGF23 and FGF2, which may correlate with drug response. The date of collection and sample IDs will be recorded on the eCRF.

5.4.2. PIIa

Blood samples (2 x 5ml) will be collected to provide one sample of plasma and one sample of serum per time point, as indicated in Table 2. These will be analysed for a range of oncology biomarkers, which may correlate with drug response. The date of collection and sample IDs will be recorded on the eCRF.

5.5. Exploratory Research

5.5.1. Biomarker research

Where a patient agrees to take part in the exploratory research aspect of the study, biological samples e.g. archived and study-specific tumour samples will be collected and may be analysed for biomarkers to investigate possible relationships with disease status, efficacy of study drug and outcome. These results may be reported separately from the clinical study report (CSR).

5.5.1.1. Collection of Archival Tumour Tissue Samples (Safety run-in)

This part of the study is optional. Where patients consent to take part, an archival tissue sample (either from the diagnostic tumour or a metastatic site) in the form of formalin fixed paraffin embedded (FFPE) tumour block will be collected. If it is not possible to obtain the entire tumour block, 10-20 slides of unstained 5 micron sections may be provided instead.

The following details will be collected: tissue obtained (yes / no), sample tissue type (primary or metastatic), whether representative tumour tissue is present, biopsy site, biopsy type, histology sample ID, whether FGFR FISH assessment was undertaken, date of assessment, FGFR1 FISH score.

5.5.1.2. Exploratory Research on Archival Tumour Tissue Samples (Phase IIa)

This part of the study is optional. Where patients consent to take part, 5-10 slides of unstained 5 micron sections will be taken from the archival tumour sample for exploratory research.

If archival tumour tissue was not available for mandatory assessment of oncology biomarkers, and a fresh tumour biopsy was obtained for this purpose (see 5.2.22), then slides form this new FFPE block may be used instead.

Further details on sample processing, handling and shipment are provided in the Study Manual.

Archival tumour blocks will be returned to source at the end of the study or, upon request, earlier if required. These samples are classified as research samples and will be registered with the Imperial College Healthcare NHS Tissue Bank (ICHTB).

The following details will be collected: whether slides taken; date slides taken and histology sample ID.

5.5.1.3. Collection of Paired Tumour Biopsies

This part of the study is optional. Where patients consent to take part, tumour biopsies should be collected prior to initiation of treatment (i.e. once the patient has been confirmed to be eligible by the RADICAL study team) and on cycle 1 day 22 (within 18 hours of administration of previous AZD4547 dose). It is strongly encouraged that at least the first biopsy is taken.

The following details will be collected: date of biopsy collection, biopsy site, biopsy type and histology sample ID.

5.5.2. Circulating Tumour Specific DNA (Phase IIa only)

Where a patient agrees to take part in the optional ctDNA study, 10 ml of blood will be collected at each of the time-points indicated in Table 2 to provide a plasma sample for ctDNA analysis. The date of collection and sample ID will be recorded on the eCRF.

The results of this research will not form part of the CSR.

5.5.3. Pharmacogenetics

Where the patient agrees to take part in the optional pharmacogenetics study, a single blood sample (1 x 5ml) will be collected to provide a plasma sample for genetic analysis. This should be obtained immediately prior to starting study treatment. The date of collection and sample ID will be recorded on the eCRF.

The results of this research will not form part of the CSR.

5.6. Chain of Custody of Biological Samples

In all cases, patients will be consented for the collection and use of their biological samples and a full chain of custody will be maintained for all samples throughout their lifecycle.

The investigator at each site is responsible for maintaining a record of full traceability of biological samples collected from patients while these are in storage at the site, either until shipment or disposal.

Any person(s) responsible for temporarily holding samples, e.g. sub-contracted service provider keeps full traceability of samples from initial receipt of sample to further shipment or disposal (as appropriate).

Imperial College keeps overall oversight of the entire lifecycle through internal procedures and monitoring of study sites

Samples retained for further use will be registered with the Imperial College Healthcare NHS Tissue Bank (ICHTB).

5.7. Total Blood Volumes

The total volume of blood that will be drawn from each patient in this study is shown in Table 4 for the safety run-in and in Table 5 for phase IIa. The number of samples taken, and the volume required for analysis, may change during the course of the study as new data becomes available.

Table 4: Volume of Blood to be Drawn from each Patient during Safety run-in

	Screening, NSAI[c] monotherapy and Cycle 1			Cycle 2 (and each subsequent cycle[b])			Treatment discontinuation / 28 day Follow-up		
	Sample volume (mL)	Number of samples	Total volume (mL)	Sample volume (mL)	Number of samples	Total volume (mL)	Sample volume (mL)	Number of samples	Total volume (mL)
Clinical chemistry[a]	6	5	30	6	1	6	6	2	12
Haematology[a]	9	5	45	9	1	9	9	2	18
Pharmaco-kinetics	5.4	18	97.2	-	-	-	-	-	-
PD biomarkers	15	5	75	-	-	-	15	1	15
Pharmaco-genetics	5	1	5	-	-	-	-	-	-
Total			**252.2**			**15**			**45**

[a] exact volume of blood for clinical chemistry and haematology may vary depending on local practice
[b] total volume in subsequent cycles may vary, but volume in any one cycle will not exceed the volume required at Cycle 2
[c] Either anastrozole or letrozole

Table 5: Volume of Blood to be Drawn from each Patient During Phase IIa

	Screening and Cycle 1			Cycle 2			Cycle 3 (and each subsequent cycle[b])			Treatment discontinuation / 28 day Follow-up		
	Sample volume (mL)	Number of samples	Total volume (mL)	Sample volume (mL)	Number of samples	Total volume (mL)	Sample volume (mL)	Number of samples	Total volume (mL)	Sample volume (mL)	Number of samples	Total volume (mL)
Clinical chemistry[a]	6	5	30	6	2	12	6	1	6	6	2	12
Haematology[a]	9	5	45	9	2	18	9	1	9	9	2	18
PD biomarkers	10	4	40	10	1	10	10	1	10	10	1	10
Pharmaco-genetics	5	1	5	-	-	-	-	-	-	-	-	-
ctDNA analysis	10	5	50	10	2	20	10	1	10	10	2	20
Total			**170**			**60**			**35**			**60**

[a] exact volume of blood for clinical chemistry and haematology may vary depending on local practice
[b] total volume in cycle 3 and subsequent cycles may vary, but volume in any one cycle will not exceed the volume required at Cycle 2

6. STUDY TREATMENT

6.1. Non Investigational Medicinal Products

Anastrozole (1mg once daily, orally) and letrozole (2.5mg once daily, orally) will be prescribed according to usual practice and dispensed from either site specific hospital stock or via the General Practitioner. Compliance to these treatments will be recorded using Patient Diary cards and all data transferred to the eCRFs.

6.2. Investigational Medicinal Product

Safety run-in: AZD4547 is manufactured by Pharmaceutical Development R&D, AstraZeneca UK according to Good Manufacturing Practice.

The investigational product is provided as, 20mg white, film-coated tablets containing AZD4547.

Phase IIa: AZD4547 is manufactured by Pharmaceutical Development R&D, AstraZeneca UK and AstraZeneca R&D Mölndal, according to Good Manufacturing Practice.

The investigational product is provided as, 20mg beige; film-coated tablets containing AZD4547.

6.2.1. Supply, Packaging and Labelling

AZD4547 will be packaged, labelled and distributed to sites by Fisher Clinical Services.
Labels will be prepared in accordance with Good Manufacturing Practice Annexe 13 requirements and local regulatory guidelines.

AZD4547 will only be dispatched to sites after receipt of confirmation that the regulatory checklist is complete.

6.2.2. Storage and Dispensing

The investigational products must be stored in a secure area with access limited to the Investigator and authorised site staff. AZD4547 film-coated tablets should be stored below 30°C in the original pack until use. Maintenance of a temperature log (manual or automated) is required. For further information investigators should refer to the investigator brochure.

The investigational product should only be dispensed and administered as directed in the protocol, and only by site staff authorised to do so i.e. pharmacist / trials technician. Only subjects enrolled in the trial may receive investigational product. AZD4547 will be dispensed at the beginning of each cycle of combination treatment.

6.2.3. Dosage and Duration

AZD4547 will be administered orally twice daily in a tablet formulation. A cycle of treatment will be defined as 28 days: one week of AZD4547 twice daily in combination with either anastrozole or letrozole once daily, followed by one week of either anastrozole or letrozole once daily alone, and the intermittent schedule repeated once more to complete one cycle.

For procedures relating to dose modification, dosing interruption and restarting of AZD4547 for subjects in both the safety run-in and phase IIa study, see 6.2.8.

6.2.3.1. Safety run-in

Dosing will begin with AZD4547 at 80 mg, twice daily given on an intermittent schedule of one week on/one week off.

Patients will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable patients per cohort. Dose de-escalation will occur according to the following conditions:

If one patient experiences a DLT in a group of 3 or more evaluable patients, then the cohort will be expanded to include 6 evaluable patients. If no more than one DLT is observed in the complete cohort of 6 evaluable patients then, with SRC review, this dose will be taken forward for the phase IIa part of the study.

If 2 or more patients experience a DLT in a group of up to 6 patients, irrespective of the number of patients enrolled, the combination dose will be considered not tolerated and recruitment to the cohort will cease. Instead, a lower intermediary combination dose (de-escalation) may be considered in order to better define the combination MTD.

There will be no intra-patient dose escalations.

The dose for subsequent cohorts or a decision to stop recruitment to the safety run-in part of the study will be agreed by the Safety Review Committee (SRC) after review of the data from each cohort. A different dose level of AZD4547 may be selected for combination with anastrozole than letrozole.

6.2.3.2. Phase IIa

The dose of AZD4547 to be used in combination with anastrozole and letrozole in the phase IIa part of the study has been determined in the safety run-in, i.e. 80 mg, twice daily given on an intermittent schedule of one week on/one week off.

N.B. If 2 or more cases of severe toxicity (leading to permanent discontinuation of study drug) are observed in the first 6 patients, an alternative schedule of two weeks on / one week off will be considered, if emerging data from other AZD4547 studies suggest that this is a better tolerated schedule. A cycle of treatment will be defined as 28 days: e.g. Cycle 1, two weeks of AZD4547 twice daily in combination with either anastrozole or letrozole once daily, followed by one week of either anastrozole or letrozole once daily alone, then one week of AZD4547 twice daily in combination with either anastrozole or letrozole once daily to complete the cycle.

6.2.4. Definition of Dose-Limiting Toxicity for assessment of safety and tolerability of AZD4547 in the safety run-in study

A DLT is defined as any toxicity not attributable to the disease or disease-related processes under investigation, which occurs after the first dose of AZD4547 at start of cycle 1 and before the end of cycle 1 (the DLT assessment window) and includes:

1. Haematological toxicity = CTCAE grade 4 present for more than 4 days
2. Non-haematological toxicity ≥ CTCAE grade 3 including:

- Infection including febrile neutropenia (Grade 3 with temperature ≥38.5°C or Grade 4 with temperature ≥38°C)
- QTc prolongation (> 500 msec) or QTc increase >60 msec from baseline

3. Any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable, does not respond to supportive care and results in a disruption of dosing schedule of more than 14 days
4. Any event, including significant dose reductions or omissions, judged to be a DLT by the SRC

A DLT excludes:

1. Alopecia of any grade
2. Isolated laboratory changes of any grade without clinical sequelae or clinical significance

6.2.5. Definition of Severe Toxicity for Assessment of Safety and Tolerability of AZD4547 in the PIIa study

For the purposes of the PIIa study, severe toxicity is defined as indicated above (6.2.4), but occurring after the first dose of AZD4547 at start of cycle 1 until study treatment discontinuation.

6.2.6. Definition of Evaluable Patient

6.2.6.1. Safety run-in

The safety run-in analysis set (SRIS) will be used for decisions on dose de-escalation and definition of dose to take forward into the phase IIa part of the study. The SRIS includes any patient that has received AZD4547 and either:

has completed minimum safety evaluation requirements and has received at least 80% of the specified dose (both AZD4547 and anastrozole / letrozole) during the first 28 day cycle

or

has experienced a DLT during the first 28 day cycle

In the safety run-in, patients that are withdrawn from the study but are deemed evaluable will not be replaced. Any patient that is withdrawn and not evaluable will be replaced to ensure the minimum number of evaluable patients is achieved.

6.2.6.2. Phase IIa

The intention-to-treat analysis set (ITTS) will be used for the efficacy analysis. The ITTS includes all study patients irrespective of drug compliance to study medication.

6.2.7. Safety Review Committee

In the safety run-in, once there are at least 3 evaluable patients at a dose level the SRC will review and assess all available safety data from the cohort together with available PK and pharmacodynamic data to make a decision on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into account. If there are still other patients that are ongoing at the time of the review, the SRC may decide to defer their decision until these further patients become evaluable.

6.2.8. Dose Modifications for AZD4547

If a patient experiences a clinically significant and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, where the Investigator considers the AE of concern to be specifically associated with AZD4547, dosing with AZD4547 will

be interrupted or the dose reduced and supportive therapy administered as required (see Figure 4 and Table 6).

If the toxicity resolves or reverts to a clinically acceptable level (at least ≤ CTCAE grade 2) within 14 days of onset and the patient is showing clinical benefit, study medication may be restarted using the rules below for dose modifications (see Figure 4) and with discussion and agreement with the Sponsor Study Team as needed.

If the toxicity does not resolve to a clinically acceptable level (at least ≤ CTCAE grade 2) after 14 days, then the patient should have study medication permanently discontinued and observed until resolution of the toxicity.

If a patient experiences a doubling of phosphate from baseline or a corrected calcium:phosphate product > 4.5mmol/L then the patient may remain on study treatment but phosphate chelation therapy (non-calcium containing agent) must be initiated, and clinical chemistry monitored weekly until resolution of the parameter to below the intervention limit. Investigators must seek appropriate specialist medical consultation (renal or metabolic) to advise on the prescription and titration of phosphate chelation agents, and to raise the patients awareness of low phosphate diets.

If patients experience toxicities regarding the anterior aspect of the eye (dry eyes, punctuate keratopathy and keratitis) such events must be clinically managed to prevent secondary consequences e.g. secondary infections following corneal abrasions. Lubricating eye drops/replacement tears should be used; if there is any indication of extra eyelash growth or eyelashes rubbing on the cornea then these eyelashes should be removed. It is anticipated that patients will report any visual disturbances or discomfort relating to the eye in advance of any significant pathology such as ulceration occurring. The decision to continue on study treatment if mild corneal changes in the eye examination are observed will be left to the Investigator's discretion, since a patient may indicate a wish to tolerate minor discomfort if there is perceived clinical benefit from the therapy. A patient should also be permanently discontinued from AZD4547 if corneal ulceration occurs, and appropriate expert ophthalmologic consultation should be initiated.

RPED has been identified in clinical studies with AZD4547 (45 occurrences as of 04 June 2014).

The prognosis is generally good if there is no actual haemorrhage from the capillaries and no evidence of any fibrovascular growth in the sub-RPE space.

An ophthalmological assessment is required if there are any of the following at any time:

- Abnormalities in the Amsler grid test
- Changes in near vision acuity
- Blurred vision
- Distortion of central vision

Subsequent management should be according to the algorithm included in Figure 5 and Figure 6. Any patients with an optical coherence tomography (OCT) scan diagnostic of RPED should be managed according to the same algorithm.

Table 6: Dose Interventions

Starting Dose	X mg bd
Reduced dose -1	X/2 mg bd
Reduced dose -2	(Reduced dose -1)/2 mg bd

Figure 4: AZD4547 Dose Modifications for Toxicity

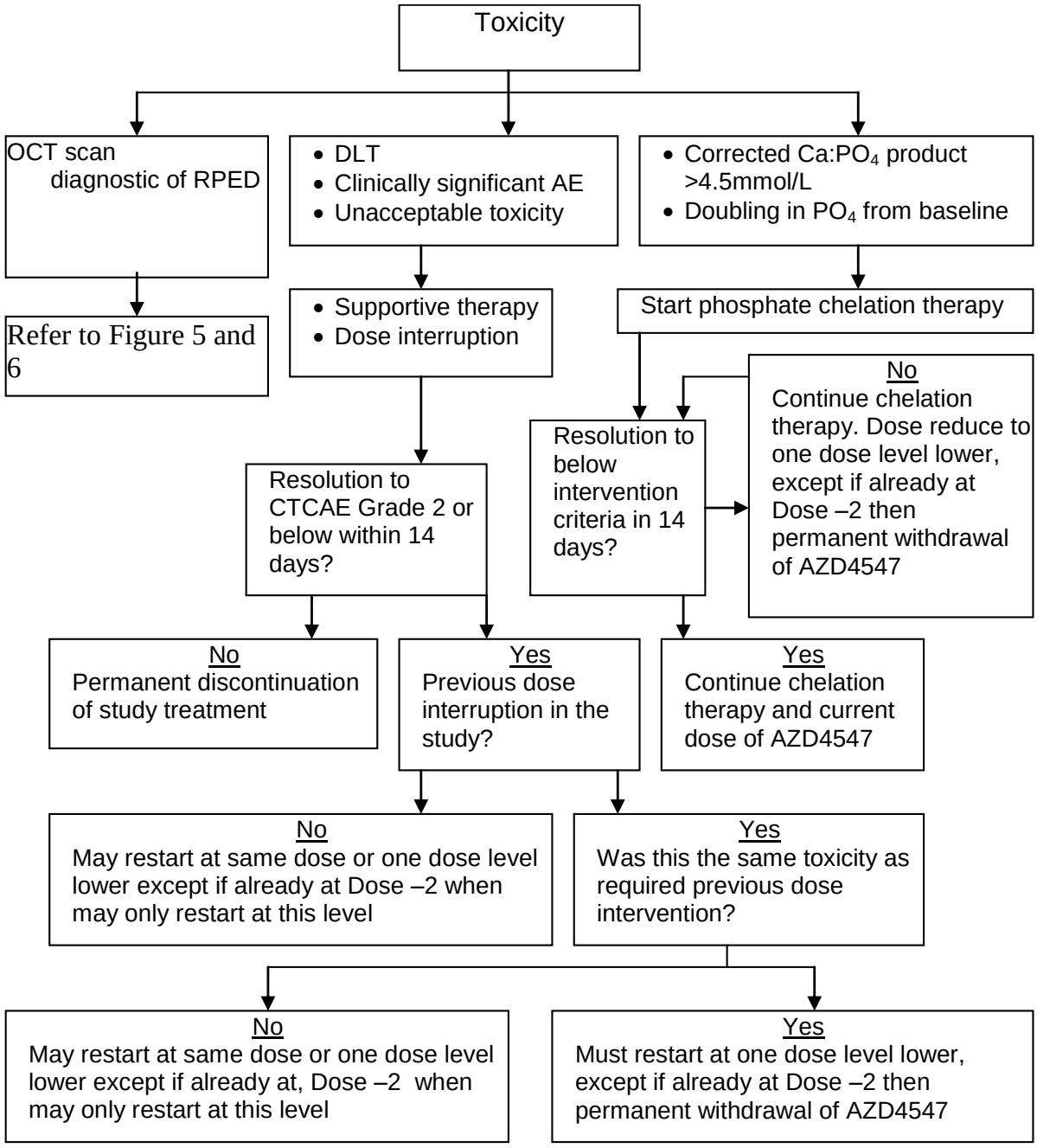
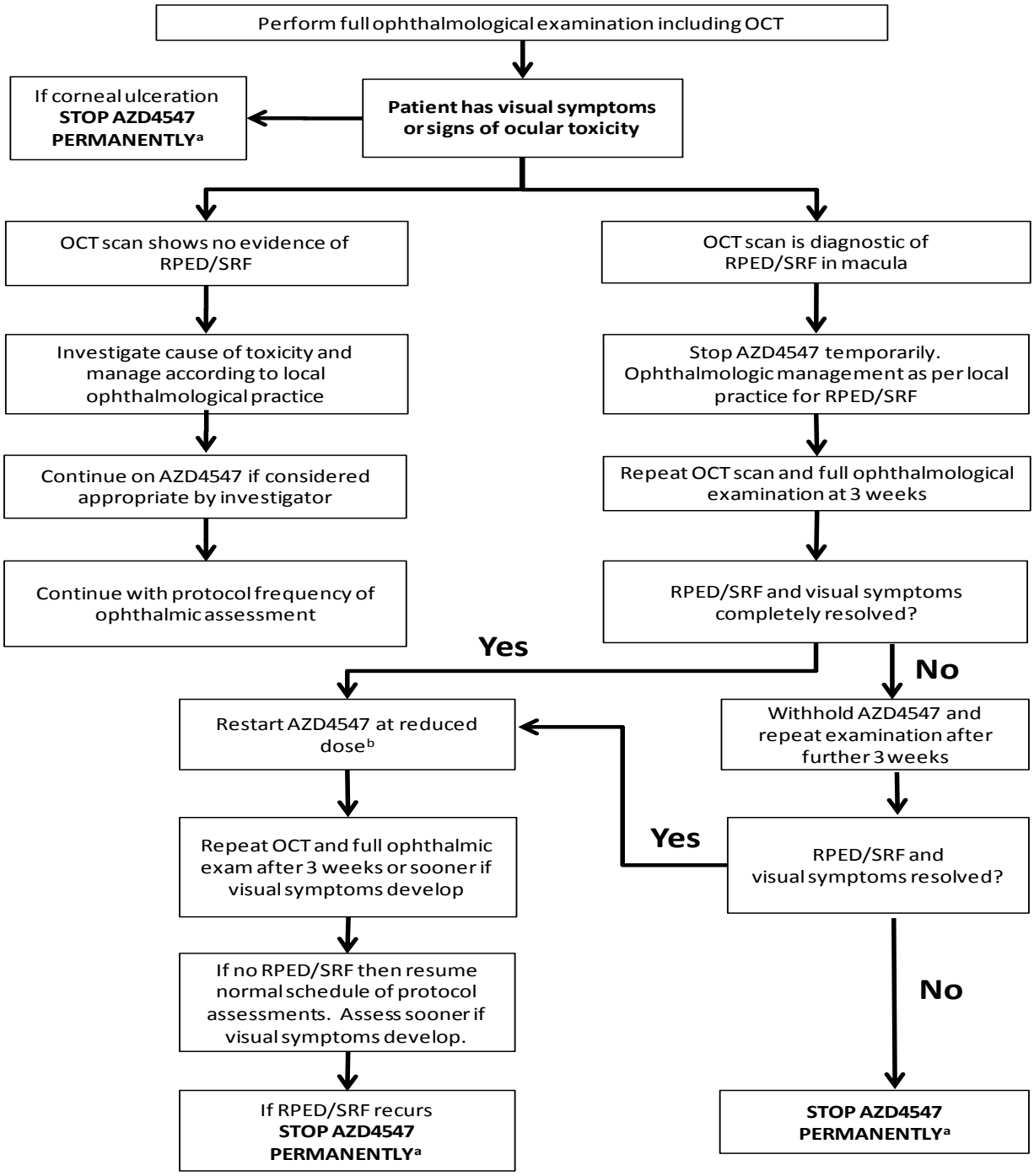


Figure 5: Management guidelines for patients with visual symptoms of ocular toxicity

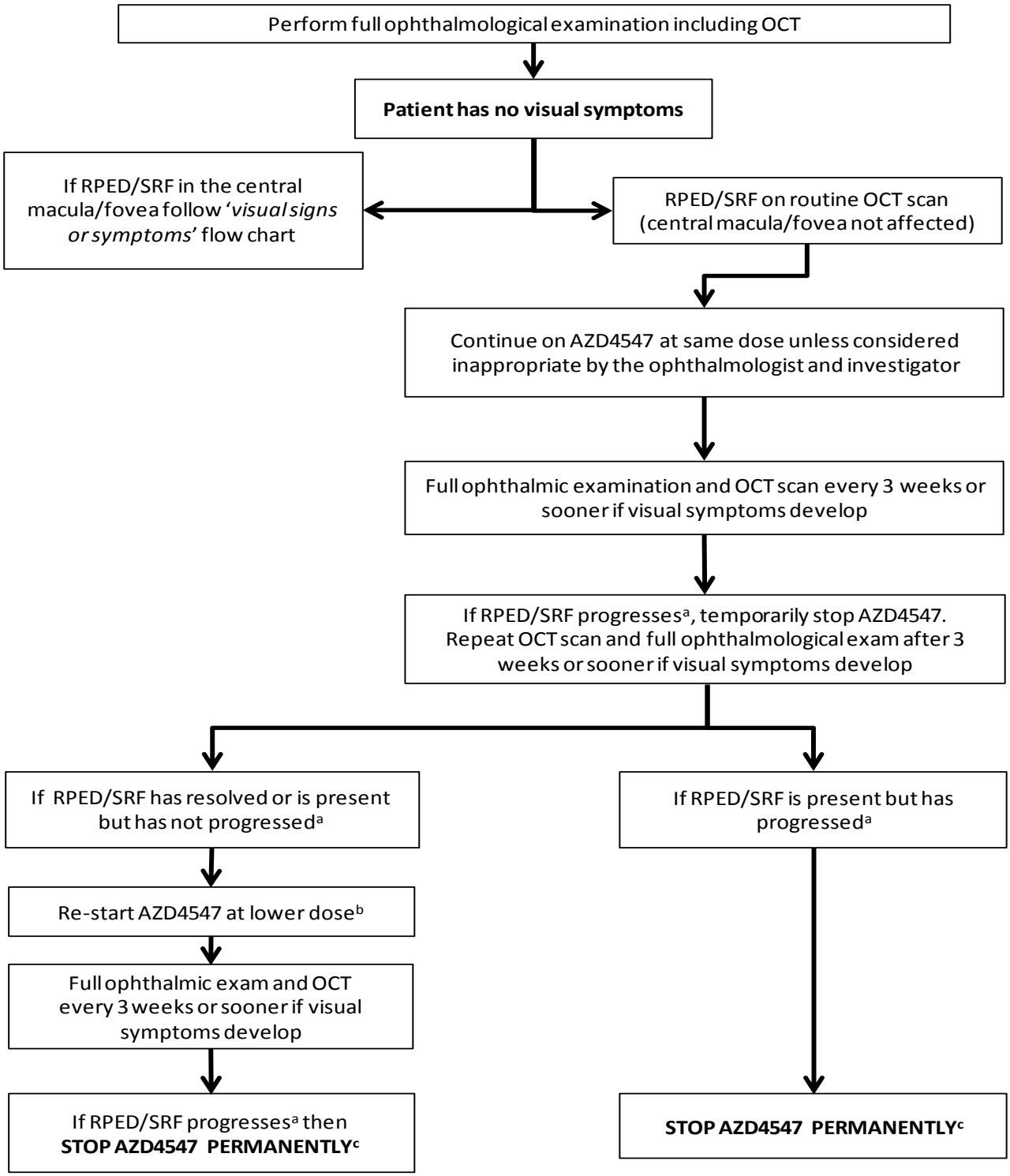


a: After permanent discontinuation of AZD4547 due to ocular toxicity, patients should be managed according to local clinical practice

b:Only 1 dose reduction allowed for management of RPED or SRF.

MedDRA Medical Dictionary for Regulatory Activities; OCT Optical-coherence-tomography; RPED or SRF This grouped term includes RPED (MedDRA preferred terms of detachment of retinal pigment epithelium and detachment of macular retinal pigment epithelium), MedDRA preferred term subretinal fluid, MedDRA preferred term serous detachment, MedDRA preferred term retinal detachment (MedDRA lower level term: serous retinal detachment); SRF Subretinal fluid

Figure 6: Toxicity management guidelines for patients with no visual symptoms of ocular toxicity



a: Progression of RPED or SRF is defined as development of visual symptoms, extension from para-macular to macula, or increase in the number of lesions.

b: Only 1 dose reduction allowed for management of RPED or SRF.

c: After permanent discontinuation of AZD4547 due to ocular toxicity, patients should be managed according to local clinical practice.

MedDRA Medical Dictionary for Regulatory Activities; OCT Optical-coherence-tomography; RPED or SRF This grouped term includes RPED (MedDRA preferred terms of detachment of retinal pigment epithelium and detachment of macular retinal pigment epithelium), MedDRA preferred term subretinal fluid, MedDRA preferred term serous detachment, MedDRA preferred term retinal detachment (MedDRA lower level term: serous retinal detachment); SRF Subretinal fluid.

6.2.9. Accountability

Patients should return all unused study medication and empty packaging to the Investigator.

A drug accountability record of the number of tablets dispensed to and returned by each subject will be maintained by the study pharmacist. This form is not part of the CRF but is maintained in the study TMF.

In accordance with local regulatory requirements, the investigator / designated site staff will document the amount of study drug received from Fisher Clinical Services, the amount (with date) dispensed to study subjects, the amount (with date) returned by study subjects and the amount destroyed locally.

Product accountability records will be maintained throughout the course of the study and filed with delivery documentation. Destruction will be documented as per local policy.

6.2.10. Compliance

The compliance of the patient will be assessed at each visit using the patient diary and the accuracy of the patient diaries will be cross checked with drug accountability records. At each visit, the cause of any missed doses should be discussed. Any AE(s) associated with missed doses must be recorded in the CRF. Subjects should be instructed on the importance of compliance to study treatments.

6.2.11. Drug Interactions/Precautions

6.2.11.1. Restrictions

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

1. All patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 or CYP2D6 enzyme activity and drugs that are known to be CYP3A4 substrates from the time they enter the screening period until 2 weeks after the last dose of study treatment. Please refer to Appendix B for further details.

2. Patients must not use oestrogen-containing agents such as hormone replacement therapy.

3. Patients with uncontrolled glaucoma or intra-ocular pressure ≥ 21mm Hg at screening should be referred for ophthalmological management and the condition controlled prior to first dose.

6.2.11.2. Concomitant Treatments

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study, with reasons for the treatment, will be recorded in the CRF. If medically feasible, patients taking regular medication, with the exception of potent inhibitors or inducers of CYP3A4 or CYP2D6 or substrates of CYP3A4, should be maintained on it throughout the study period.

Patients should not be administered calcium-containing phosphate chelation agents, such as calcium acetate, for the management of hyperphosphataemia whilst receiving study treatment due to the increased risk of precipitating ectopic tissue mineralisation.

Other anticancer agents, investigational agents and radiotherapy should not be given while the patient is on study treatment although radiation for palliation at focal sites is permitted.

Patients may receive treatment with corticosteroids and/or bisphosphonates for the treatment of bone metastases.

Patients may take warfarin or a coumarin preparation but it is recommended that they should have their anticoagulation monitored carefully and dose adjusted accordingly.

Supportive care and other medications that are considered necessary for the patient's well-being may be given at the discretion of the Investigator.

6.2.12. Overdose of IMP

There is no known antidote to AZD4547. Investigators should be advised that any patient who receives a higher dose of AZD4547 than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

If an overdose of AZD4547 occurs in the course of the study, then Investigators or other site personnel should inform the Sponsor **within one day** i.e. immediately and no later than **the end of the next business day** of when he or she becomes aware of it.

For overdoses associated with a SAE, standard reporting timelines apply. For other overdoses, reporting should be done within 30 days.

For treatment of overdose with anastrozole / letrozole please refer to the local prescribing information. Overdose of anastrozole or letrozole with associated AEs / SAEs should be recorded in the relevant AE / SAE module of the eCRF and reported according to the standard timelines.

6.3. Permanent Discontinuation of Study Medication and Withdrawal from Study

6.3.1. Permanent Discontinuation of Study Medication

A patient may be permanently discontinued from study medication for the following reasons:

- Patient decision
- Significant adverse events or unacceptable toxicities
- Severe non-compliance to this protocol as judged by the Investigator
- Confirmed disease progression
- Allergic reaction to study medication
- If the investigator considers that a subject's health will be compromised due to adverse events or concomitant illnesses that develop after entering the study.

Date of permanent discontinuation and the reason will be recorded.

Once study medication is permanently discontinued it cannot be restarted.

6.3.2. Withdrawal from Study

Withdrawal from the study refers to discontinuation of both study medication and study participation; this can occur at any time according to the following reasons:

- Patient decision
- Lost to follow-up
- Death
- Investigator decision

If a patient dies whilst participating in the study a “Statement of Death” CRF must be completed. The following details will be collected: date of death, whether autopsy performed, whether death was related to the disease under investigation, primary cause of death, secondary cause of death, and any other details.

6.3.3. Procedures for Withdrawal from Study

If the patient is withdrawn from the study the date of withdrawal and the reason must be recorded. If possible, the investigator should arrange for the end of study assessments to be completed. Where the patient has withdrawn due to an AE, the investigator should follow the procedures in section 7.0.

7. PHARMACOVIGILANCE

7.1. Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence (including deterioration of a pre-existing medical condition) in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign including abnormal results of an investigation (e.g. laboratory finding, electrocardiogram), symptom(s) (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or disease temporally associated with the use of the trial medication.

7.1.1. Disease Progression

Disease progression is a worsening of a patient's condition attributable to the disease for which the study medication is being given. This may be an increase in severity of the disease or increase in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. **Events that are unequivocally due to disease progression should not be reported as AEs during the study**.

7.1.2. New Cancers

The development of a new cancer should be regarded as an AE and reported accordingly. Generally, it will also meet at least one of the serious criteria.

7.2. Recording of Adverse Events

AEs will be collected throughout the study, from the point that the RADICAL team have confirmed patient eligibility, via e-mail (and the study entry eCRF has been completed by the RADICAL team) until the end of follow-up; they will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner*. Serious Adverse Events (SAEs) will also be recorded throughout the study.

Any AEs which remain unresolved at the patient's last visit in the study should be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.*

***N.B. Any ophthalmic AEs will be followed up until event resolution or stabilisation (or until the trial closes if event is on-going at the end of trial) and should be recorded in the eCRF.**

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to AZD4547, the Investigator should notify the trials unit.

The following details will be collected in the CRF for each AE:

- AE description / diagnosis
- Date of onset and date of resolution
- CTCAE grade maximum intensity
- Seriousness
- Investigator causality rating against the study medication (yes or no)
- Action taken with regard to study medication
- Outcome

7.3. Severity of Adverse Events

Severity is a measure of intensity whereas seriousness is defined by the criteria in section 7.6. Severity will be assessed using the grading scales found in the National Cancer Institute CTCAE version 4.02 (September 2009) for all adverse events with an assigned CTCAE term. For those events without assigned CTCAE grades, the recommendation on page 1 of the CTCAE that converts mild, moderate and severe into CTCAE grades should be used. A copy of the CTCAE version 4.02 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

7.4. Causality of Adverse Events

The Investigator will assess causal relationship between the investigational product and the combination treatment and each AE.

Unassessable: There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship

Unrelated: No evidence of any causal relationship

Unlikely: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.5. Abnormal Laboratory Test Results

All clinically important abnormal laboratory test results occurring during the study will be recorded as adverse events. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made.

7.6. Definitions of Serious Adverse Events (SAE)

An SAE is an AE occurring during any part of the study that meets one or more of the following criteria:

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).
Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

7.7. Reporting of SAEs

Rapid reporting, within 24 hours of the Principal Investigator or designee becoming aware of the event, of all SAEs occurring during the study or within 28 days following the completion of the study treatment by the subject, must be performed as detailed in the "SAE reporting instructions". If the investigator becomes aware of safety information that appears to be drug related, involving a subject who participated in the study, even after an individual subject has completed the study, this should also be reported to the Sponsor.

The SAE should be reported electronically to the study team at the Imperial Clinical Trials Unit – Section on Cancer via the RADICAL database as detailed in the Pharmacovigilance study manual.

All SAEs will be reviewed by the Chief Investigator or designated representative to confirm relatedness and expectedness.

Following documented assessment by the CI, the completed SAE form will be sent by e-mail to AstraZeneca and the Sponsor by the study team at ICTU-Ca within the pre-specified timelines.

7.8. Definition of a Serious Adverse Reaction (SAR)

A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the subject.

7.9. Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Investigator Brochure (IB) or Summary of Product Characteristics (SPC).

7.10. Reporting of SUSARs

SUSARs will be notified to the appropriate regulatory authority, the relevant Independent Ethics Committee (IEC) / Institutional review board (IRB), AstraZeneca, the Sponsor and the participating Principal Investigators by ICTU-Ca in accordance with regulatory requirements.

Follow up of patients who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised.

7.11. Annual Reporting of Serious Adverse Reactions

Annual reports will be submitted to the MHRA and main REC by ICTU-Ca according to current requirements.

8. STATISTICAL ANALYSES

8.1. Sample Size and Power Considerations

For the primary analysis, a 95% two-sided confidence interval will be calculated for change in tumour size at 12 weeks. With 50 patients, assuming a standard deviation (SD) of 0.30* for the change in log transformed tumour size, the confidence interval for the mean on the log scale will extend 0.083 from the observed mean in either direction. On the natural scale, the 95% confidence interval for the observed geometric mean will extend 1.09 in either direction. This sample size should also be sufficient for the secondary and exploratory analyses to be performed.

*Our estimate of the SD is based on previously collected data, which showed that the standard deviation of logarithmically transformed tumour size at 12 weeks is 0.30. Since we would expect the SD of change in logarithmically transformed tumours size to be somewhat smaller than the SD of log transformed tumour size at 12 weeks, we feel that the above estimate of the width of the confidence interval is very conservative.

8.2. Data Analysis

8.2.1. Interim Analysis

An interim analysis will occur after 20 patients are recruited into the study (including patients in the safety run in phase) and have completed their 12-week follow up. Following recommendations from the Independent Data Monitoring Committee (IDMC) data will also be reviewed once 20 patients (including patients in the safety run in phase) have completed their 20-week follow up. Recruitment into the study will continue whilst the analysis is being carried out.

≥30% will be considered as the 12/20-week clinical benefit rate (stable disease, partial response, complete response) of interest and ≤5% as non-significant 12/20-week clinical benefit rate. With power of 85% and type I error of one-sided 0.05, the study will continue if 4 or more patients out of 20 show clinical benefit. If less than 4 patients show clinical benefit the study will only continue if a particular biomarker has been identified.

8.2.2. Preliminary Final Analysis

Since the study has follow up of efficacy and safety endpoints beyond 12 weeks, the preliminary final analysis may be conducted as soon as the database can be soft locked for the primary endpoint data accumulated up to 12 weeks after the last subject enters the study.

The analysis of primary endpoint, i.e. change in tumour size at 12 weeks (or progression if prior to week 12), will be performed on completed cases only. To assess the effect of early drop out (due to death or withdrawal before 12 week follow up scan or progression, for example) change in tumour size at 6 weeks will also be calculated and the results compared to the primary analysis. Subjects with only baseline measures will be excluded from the analysis.

The study data will be summarised using standard descriptive methods. Histograms and box-plots will be used to assess the distributional assumptions and to check for possible outliers. Mathematical transformations will be applied, where appropriate, in order to render variables normally distributed. Continuous variables that follow an approximately normal distribution will be summarised using the mean and standard deviation. Skewed continuous variables will be summarised using the median and inter-quartile range. Categorical variables (binary, ordered and multinomial) will be presented in terms of frequencies and percentages. Where possible, the relationship between the outcomes and other variables will be explored graphically, using scatter plots and box-plots prior to model fitting. Change in tumour size at 12 weeks for each patient will

be shown graphically in a “waterfall plot” with subgroups based on tumour response and objective response highlighted in different colours to identify possible patterns.

The comprehensive statistical analysis plan (SAP) will be finalised prior to preliminary final analysis.

8.2.3. Final Analysis

The final analysis will be conducted after the collection of the last data point for the last patient (i.e. study end). The final analysis will be an addendum of the preliminary final analysis for any data collected since the time of the previous analysis.

8.2.4. Missing, Unused and Spurious Data

Safety run-in

There will be no data imputation for missing data in the primary endpoint (DLTs). Procedures for accounting for missing, unused and spurious PK concentration-time data will be determined by the PK parameter derivation rules of the PK scientist. The PK parameter derivation rules will not be documented in the SAP.

Phase IIa

For the primary analysis, there will be no data imputation for missing data in the primary endpoint.

Imputation methods may be proposed for purposes of sensitivity analysis. Imputation methods for missing data in the primary endpoint and secondary endpoints will be fully documented in the SAP, if any.

8.2.5. Deviations from the Statistical Plan

Any deviation(s) from the final statistical plan in the final analysis will be described and justification given in the final report.

8.2.6. Efficacy Analysis

All patients will be included in the efficacy analysis.

To be considered ‘evaluable’ for the primary efficacy analysis, a patient must have a week 12 (± 1 week) tumour measurement or evidence of progression prior to week 12.

8.2.7. Primary Analysis

The primary endpoint of change in tumour size at week 12 (or progression if prior to week 12) will be assessed in all patients. The data cut-off for the primary endpoint will occur 12 weeks after the last subject has entered the study.

8.2.8. Secondary Analyses

Frequency tabulations of the tumour response RECIST criteria and 2-category ORR will be presented.

As median time to progression is expected to be 6 months and the recruitment period to be 24 months, the analysis of PFS will take place at 30 months (when each subject has been followed up to progression or for a minimum of 6 months). At this time we anticipate that 95% of subjects will have progressed on study treatment.

8.2.9. Safety Analysis

All patients who receive at least one dose of study treatment will be included in the safety analysis set. Safety data will not be formally analysed. Safety and tolerability data will be presented by treatment received.

9. REGULATORY, ETHICAL AND LEGAL ISSUES

9.1. Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the principles of the 1964 Declaration of Helsinki and any subsequent revisions.

9.2. Good Clinical Practice

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3. Independent Ethics Committee/Institutional Review Board Approval

9.3.1. Initial Approval

Prior to the shipment of IMP and the enrolment of subjects, the IEC/IRB must provide written approval of: the conduct of the study at named sites, the protocol and any amendments, the Subject Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation.

9.3.2. Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the IEC/IRB for approval. Amendments requiring IEC/IRB approval may be implemented only after a copy of the IEC/IRB's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or IEC/IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

9.3.3. Annual Safety Reports and End of Trial Notification

The IEC/IRB will be sent annual safety updates in order to facilitate their continuing review of the study (reference. ICH GCP E6 Section 3.1.4) and will also be informed about the end of the trial, within the required timelines.

9.4. Regulatory Authority Approval

The study will be performed in compliance with the regulatory requirements of the United Kingdom. Clinical Trial Authorisation from the appropriate Regulatory Authority must be sought/obtained prior to the start of the study. In addition, the Regulatory Authority must approve amendments (as instructed by the Sponsor), receive SUSAR reports and annual safety updates, and be notified of the end of the trial.

9.5. Insurance

The Sponsor has civil liability insurance, which covers this study in the United Kingdom.

9.6. Informed Consent

The Principal Investigator at each site will:

- Ensure that each patient is given full and adequate oral and written information about the study including the background, purpose and risks/benefits of participation
- Ensure that each patient is notified that they are free to withdraw from the study at any time

- Ensure that each patient is given the opportunity to ask questions and allowed sufficient time to read and understand the information sheet
- Ensure each patient provides signed, dated informed consent before undergoing any study specific procedure
- Ensure the original copy of the signed, dated Informed Consent Form is stored in the patient's medical records and a copy is also filed in the Investigator site file
- Ensure that each patient receives a copy of the signed, dated Informed Consent Form

9.7. Contact with General Practitioner

It is the investigator's responsibility to inform the subject's General Practitioner (where applicable) by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Subject Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

9.8. Subject Confidentiality

The investigator must ensure that the subject's privacy is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a trial ID number only. Documents that are not submitted to the Sponsor (e.g. signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Regulatory Authorities and IECs / IRBs.

9.9. Data Protection

Precautions will be taken to ensure that patient confidentiality is preserved at all times. The Patient Consent form will identify those individuals who will require access to patient data and identifiable details and obtain appropriate permission from the consenting patient.

9.10. End of Trial

The end of the trial is defined as collection of the last data point for the last patient.

9.11. Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor (Imperial College London), and at least for ten years after study completion, as per Imperial College London policy. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA AND STUDY MANAGEMENT

10.1. Source Data

All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial are classified as source data. Source data are contained in source documents; these are defined as: original documents, data, and records e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

10.2. Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

10.3. Data Collection

In compliance with Good Clinical Practice (GCP), the medical records/medical notes should be clearly marked and allow easy identification of a patient's participation in the clinical trial

The Investigator (or delegated member of the site study team) must record all data relating to protocol procedures, IMP administration, laboratory data, safety data and efficacy data into the trial InForm electronic data collection (EDC) system.

10.4. Electronic Recording of data

Full details for procedures for completion of eCRFs will be provided in the study manual.

10.5. Data Management

Data management will be performed by the Imperial Clinical Trials Unit – Section on Cancer using the InForm electronic data capture (EDC) and management system. The system allows for real time oversight of trial activity including adverse event reporting, rapid data validation and data aggregation.

AE data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, and CTCAE grade.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trial.

10.6. Study Management Structure

10.6.1. Trial Steering Committee

The Trial Steering Committee (TSC) convened for the safety run-in part of the study, will continue their role in the phase IIa part of the study. The TSC includes: an independent Chair; two independent clinicians; a patient representative; the Chief Investigator and Trial Coordinator. The role of the TSC will be to provide overall supervision of the trial including monitoring progress, adherence to the protocol and patient safety. It will also consider new information relevant to the

research question as it becomes available and as necessary, advise the TMG on operational issues.

Where possible, membership will also include a lay/consumer representative

10.6.2. Trial Management Group

The Trial Management Group (TMG) convened for the safety run-in part of the study, will continue their role in the phase IIa part of the study. The TMG includes: the Chief Investigator, co-investigators and identified key collaborators, the trial statistician and trial co-ordinator. Principle Investigators and key study personnel may be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups.

Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will have operational responsibility for the day to day conduct of the trial.

10.6.3. Safety Review Committee (Safety run-in only)

The Safety Review Committee (SRC) will consist of the Chief Investigator, the Trial Coordinator and local investigators or delegates from each actively recruiting site. An AstraZeneca Medical Science Director and a Medical Advisor from Cancer Research UK's Drug Development Office will also be invited to attend. The ICTU-Ca Senior Trials Manager and Study Statistician may attend as appropriate. The committee will evaluate safety data acquired during the safety run-in part of the study only, and make recommendations on dose de-escalation / modification decisions in the safety run-in phase and confirm the dose to take forward to the phase IIa part of the study.

10.6.4. Independent Data Monitoring Committee (Phase IIa only)

An Independent Data Monitoring Committee (IDMC) will be convened to monitor data collected during the phase IIa part of the study only, and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue. It will consist of an independent Chair, an independent statistician and an independent clinician.

10.7. Monitoring

The study will be monitored periodically by monitors in the UK to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan. Monitoring will be proportionate to the objective, purpose, design, size, complexity, blinding, endpoints and risks associated with the clinical trial. The appropriate level and nature of monitoring required for the clinical trial will be assessed by undertaking a formal risk assessment analysis of the study.

10.8. Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

10.9. Disclosure of Data and Publication

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting, should only be undertaken with written consent from the Sponsor.

Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) is completed.

Investigators may only present data separately to the total data available, with the permission of the TMG, and not less than 6 months after the publication of the main results.

AstraZeneca has the right to review all abstracts, papers or other research communications prior to their submission to journals, meetings or conferences.

11. REFERENCES

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3. Cardoso F, Castiglione M: Locally recurrent or metastatic breast cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 20 Suppl 4:15-8, 2009

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12. SIGNATURE PAGES

SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory.

I agree to the terms of this study protocol. I will conduct the study according to all stipulations of the protocol including all statements regarding confidentiality, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Study Title: A single arm phase IIa study (with combination safety run-in) to assess the safety and efficacy of AZD4547 in combination with either anastrozole or letrozole in ER positive breast cancer patients who have progressed on treatment with anastrozole or letrozole - **RADICAL**

Protocol Number: C/23/2011

Signed:

Michael J Seckl
Professor of Molecular Cancer Medicine

Date: 16/11/2016

SIGNATURE PAGE 2 (Sponsor)

The signature below constitutes approval of this protocol by the signatory.

Study Title: A single arm phase IIa study (with combination safety run-in) to assess the safety and efficacy of AZD4547 in combination with either anastrozole or letrozole in ER positive breast cancer patients who have progressed on treatment with anastrozole or letrozole - **RADICAL**

Protocol Number: C/23/2011

Signed: _____

Gary Roper
Head of Regulatory Compliance
Imperial College London

Date: 26.09.14.

SIGNATURE PAGE 3 (STUDY STATISTICIAN)

The signature below constitutes approval of this protocol by the signatory.

Study Title: A single arm phase IIa study (with combination safety run-in) to assess the safety and efficacy of AZD4547 in combination with either anastrozole or letrozole in ER positive breast cancer patients who have progressed on treatment with anastrozole or letrozole - **RADICAL**

Protocol Number: C/23/2011

Signed: _____

Xinxue Liu
Study Statistician
Imperial College London

Date: 22/11/2016

SIGNATURE PAGE 4 (INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: A single arm phase IIa study (with combination safety run-in) to assess the safety and efficacy of AZD4547 in combination with either anastrozole or letrozole in ER positive breast cancer patients who have progressed on treatment with anastrozole or letrozole - **RADICAL**

Protocol Number: C/23/2011

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

13. APPENDICES

Appendix A: Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

(ICTU-Cancer guidance document v2.0 dated 17 November2014)

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumours (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumour lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definition of Disease Parameters

Measurable disease Must be accurately measured in a least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5mm; when CT scans have slice thickness >5mm, the minimum size should be twice the slice thickness).
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measureable).
- 20mm by chest X-ray.

Note: Tumour lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measureable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Malignant lymph nodes Criteria for lymph nodes given as ≥15mm short axis for target lesions and 10mm to <15mm for non-target lesions. Nodes under 10mm to be considered non-pathological.

Non-measurable disease All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include; leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Note: Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.

'Cystic lesions' thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements. All measurements should be recorded in metric notation

using calipers if clinically assessed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters, which will be used as reference to further characterize any objective tumour regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

Non-target lesions All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

Methods of Measurement

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

CT/MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g. for body scans but not for lung).

Chest x-ray Lesions on chest x-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial and ≥10mm in diameter as assessed using calipers. For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is recommended.

Ultrasound (US) should not be used to measure tumour lesions.

Tumour markers Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology Can be used in rare cases (e.g. for evaluation of residual masses to differentiate between Partial Response and Complete Response or evaluation of new or enlarging effusions to differentiate between Progressive Disease and Response/Stable Disease).

Endoscopy, Laparoscopy Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.

New Lesions

It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is no PD.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumour marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis)

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- When patient has measurable disease – to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-

target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

- When patient has none-measurable disease – there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localised to widespread.

Evaluation of Best Overall Response

Summary of overall response status calculation at each time point, for patients who have measurable disease at baseline.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
Not all evaluated	Non-PD	No	Not evaluated	
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, (taking as reference for PD the smallest measurements recorded on study).

Duration of stable disease: SD is measured from the start of the treatment (in randomised trials, from the date of randomization) until the criteria for disease progression are met, taking as reference the smallest sum on study (if baseline sum is the smallest, this is the reference for calculation of PD).The clinical relevance of the duration of SD varies for different studies and diseases. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Response Review

For trials where the objective response (CR and PR) is the primary endpoint it is recommended that all responses be reviewed by an expert(s) independent of the study. Simultaneous review of the patients' files and radiological images is the best approach.

Appendix B:

Guidance on Potential Interactions with Concomitant Medications (dated 9th July 2010)*

***The appendix should not be taken as a definitive list. All conmeds should be checked locally for Drug Drug Interactions by checking the Summary of Product Characteristics for each drug. This information is publically available online (http://www.medicines.org.uk).**

1. Drugs affecting CYP3A4 or CYP2D6 metabolism that AstraZeneca strongly recommend are not combined with AZD4547

Table 1: Potent CYP3A4 or CYP2D6 inhibitors may increase exposure to AZD4547 more than 5-fold

Fluoxetine	Minimum of 35 days washout prior to AZD4547 administration and for 14 days following discontinuation of AZD4547
Ketoconazole Ritonavir Saquinavir Indanavir Nefazodone Nelfinavir Paroxetine Quinidine	Minimum of 2 weeks washout prior to AZD4547 administration and for 2 weeks following discontinuation of AZD4547
Itraconazole Clarithromycin (250mg or 500mg bd)	Minimum of 1 week washout prior to AZD4547 administration and for 2 weeks following discontinuation of AZD4547

Table 2: Potent Inducers of CYP3A4 may reduce exposure to AZD4547 by more than 3-fold

Barbiturates Carbamazepine Phenytoin Rifampicin, Rifabutin Troglitazone	Minimum of 2 weeks washout prior to AZD4547 administration and for 2 weeks following discontinuation of AZD4547
St John's Wort	Minimum of 3 weeks washout prior to AZD4547 administration and for 2 weeks following discontinuation of AZD4547

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and AZD4547; a potential interaction is considered on the basis of preclinical data only. This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 or CYP2D6 activity. Appropriate medical judgment is required. Please contact the study coordinator at ICTU-Cancer with any queries you have on this issue.

2. <u>Drugs affecting CYP3A4 metabolism that AstraZeneca considers may be allowed with caution</u>

Table 3: Moderate Inhibitors of CYP3A4 or CYP2D6 may increase exposure to AZD4547

Warning of possible interaction	
Aprepitant Diltiazem Duloxetine Erythromycin Fluconazole Sertraline Terbinafine Verapamil	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD4547.
Grapefruit juice Seville oranges (and other products containing Seville oranges)	Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g., grapefruit juice or marmalade) during the study (i.e. no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15 g) of Seville orange marmalade daily).

3. <u>Medicines that are significantly metabolised by CYP3A4 that AstraZeneca strongly recommend are not combined with AZD4547</u>

Table 4: Exposure, pharmacological action and toxicity may be increased by inhibition of CYP3A4 by AZD4547

Alfentanil Cyclosporin Tacrolimus Atorvastatin Lovastatin Simvastatin	Minimum of 1 week washout prior to AZD4547 administration and for 2 weeks following discontinuation of AZD4547
Carbamazepine	Minimum of 2 weeks washout prior to AZD4547 administration and for 2 weeks following discontinuation of AZD4547.

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and AZD4547; a potential interaction is considered on the basis of preclinical data only. This list is not intended to be exhaustive, and a similar restriction will apply to other agents with narrow therapeutic windows that are known to depend on CYP3A4 for metabolism. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

4. MEDICINES THAT ARE SIGNIFICANTLY METABOLISED BY CYP3A4 THAT STRAZENECA CONSIDERS MAY BE ALLOWED WITH CAUTION

Table 5: Exposure, pharmacological action and toxicity may be increased by inhibition of CYP3A4 by AZD4547

Warning of possible interaction:	
Alprazolam Erythromycin Felodipine Isradipine Midazolam Nifedipine Tamoxifen Trazodone Triazolam And possibly other calcium antagonists Methylprednisolone Pimozide Quinidine	Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD4547.

5. Drugs that may prolong QT interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland.

Ref: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm

5.1 Drugs known to prolong QT interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with AZD4547. Recommended washout periods following cessation of treatment with these agents are provided in the following table.

Contraindicated drug	**Washout period prior to AZD4547 start**
Droperidol	2 days
Erythromycin	
Procainamide	
Cisapride	7days
Clarithromycin	
Disopyramide	
Dofetilide	
Domperidone*	

Contraindicated drug	Washout period prior to AZD4547 start
Ibutilide	
Quinidine	
Sotalol	
Sparfloxacin	
Thioridazine	
Bepridil	14 days
Chlorpromazine	
Halofantrine	
Haloperidol	
Mesoridazine	
Levomethadyl	4 weeks
Methadone	
Pimozide	
Arsenic trioxide	6 weeks*
Pentamidine	8 weeks
Amiodarone	1 year
Chloroquine	

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

5.2 Drugs that may possibly prolong QT interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the patient has been stable on therapy for the periods indicated.

Warning of possible interaction	
Drug	**Minimum treatment period on medication prior to AZD4547 start**
Alfuzosin	2 days
Chloral hydrate	
Ciprofloxacin	
Dolasetron	
Foscarnet	
Galantamine	
Gemifloxacin	
Isradipine	
Ketoconazole	
Levofloxacin	
Mexiletine	
Nicardipine	

Warning of possible interaction	
Drug	**Minimum treatment period on medication prior to AZD4547 start**
Octreotide	
Ofloxacin	
Ondansetron	
Quetiapine	
Ranolazine	
Telithromycin	
Tizanidine	
Vardenafil	
Venlafaxine	
Ziprasidone	
Amantadine	7 days
Amitriptyline	
Amoxapine	
Clozapine	
Doxepin	
Felbamate	
Flecainide	
Fluconazole	
Fosphenytoin	
Gatifloxacin	
Granisetron	
Imipramine	
Indapamide	
Lithium	
Moexipril/HCTZ	
Moxifloxacin	
Risperidone	
Roxithromycin	
Sertraline	
Trimethoprim-Sulfa	
Trimipramine	
Voriconazole	
Azithromycin	14 days
Citalopram	
Clomipramine	

Warning of possible interaction	
Drug	**Minimum treatment period on medication prior to AZD4547 start**
Itraconazole	
Nortriptyline	
Paroxetine	
Solifenacin	
Tacrolimus	
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks